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Item 5 (b) (i) of the provisional agenda*

Technical work: consideration of draft risk profiles: dicofol

Draft risk profile: dicofol

Note by the Secretariat

I. Introduction

1. At its tenth meeting, the Persistent Organic Pollutants Review Committee adopted decision POPRC-10/3 on dicofol (see UNEP/POPS/POPRC.10/10, annex I). By paragraph 2 of that decision, the Committee decided to establish an intersessional working group to further review the proposal to list dicofol in Annexes A, B and/or C to the Stockholm Convention on Persistent Organic Pollutants (UNEP/POPS/POPRC.10/4) and to prepare a draft risk profile in accordance with Annex E to the Convention.

2. In accordance with decision POPRC-10/3 and the workplan for the preparation of a draft risk profile adopted by the Committee (UNEP/POPS/POPRC.10/10, annex III), the intersessional working group has prepared a draft risk profile, which is set out in the annex to the present note, without formal editing. A compilation of comments and responses relating to the draft risk profile is set out in document UNEP/POPS/POPRC.11/INF/8.

II. Proposed action

3. The Committee may wish:

(a) To adopt, with any amendments, the draft risk profile set out in the annex to the present note;

(b) To decide, in accordance with paragraph 7 of Article 8 of the Convention and on the basis of the risk profile, whether dicofol is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and/or environmental effects, such that global action is warranted;

(c) To agree, depending on the decision taken under subparagraph (b) above:

(i) To invite all parties and observers to provide information pursuant to Annex F to the Convention, to establish an intersessional working group to develop a draft risk management evaluation and to agree on a workplan for completing that draft evaluation; or

(ii) To make the risk profile available to all parties and observers and set it aside.

* UNEP/POPS/POPRC.11/1.

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Annex

DICOFOL

DRAFT RISK PROFILE

Prepared by the intersessional working group on dicofol
Persistent Oranic Pollutants Review Committee

July 2015

Table of Contents

Executive summary 4

1. Introduction 5
   - 1.1 Chemical identity 6
   - 1.2 Conclusion of the Review Committee regarding Annex D information 7
   - 1.3 Data sources 7
   - 1.4 Status of the chemical under international conventions 8

2. Summary information relevant to the risk profile 8
   - 2.1 Sources 8
     - 2.1.1 Production, trade, stockpiles 8
     - 2.1.2 Uses 9
     - 2.1.3 Releases to the environment 10
   - 2.2 Environmental fate 10
     - 2.2.1 Persistence 10
     - 2.2.2 Bioaccumulation 13
     - 2.2.3 Potential for long-range environmental transport 15
   - 2.3 Exposure 16
     - 2.3.1 Environmental monitoring data 16
     - 2.3.2 Human Exposure 18
   - 2.4 Hazard assessment for endpoints of concern 20

3. Synthesis of information 25

4. Concluding statement 28

5. References 29

Executive summary

1. Dicofol is an organochlorine pesticide consisting of two isomers (p,p'-dicofol and o,p'-dicofol). Technical dicofol is composed of 80-85% p,p'-dicofol and 15-20% o,p'-dicofol with a reported variation range of DDT and other impurities. In several countries regulations exist with respect to the ΣDDT content of commercial dicofol. The FAO Specification 123/TC/S/F (1992) requires ΣDDT to be less than 0.1%. In Australia, Brazil, Canada, Japan, EU, and USA the limit is 0.1%. Dicofol has been sold from the mid-1950s as a miticidal pesticide and acaricide and has been used primarily in East and Southeast Asia, the Mediterranean coast, as well as in Northern and Central America. Dicofol is restricted or prohibited in many countries and usage has markedly decreased in the last decade (approximately 80% from the years 2000 to 2012).

2. Although laboratory data indicate that dicofol will not persist in water or sediment under neutral or alkaline conditions because of rapid hydrolysis at these pH values both isomers are stable under acidic conditions. Governmental assessment summaries showed a wide range of reported degradation half-lives in soil simulation tests, and some of them exceed 180 days. Field soil dissipation studies from Florida and California reported dissipation half-lives in the range of 7 to 113 days for dicofol. Experimental evidence suggests that abiotic as well as biotic degradation are dependent on the pH value of the receiving environmental compartment with longer degradation half-lives under acidic conditions. Several laboratory studies reported low mineralisation of dicofol.

3. The UN ECE Task Force on POPs under the Convention on Long-range Transboundary Air Pollution concluded that dicofol is persistent in acidic water and meets the persistency indicative numerical value of EB decision 1998/2. It can be anticipated that dicofol and/or its degradates (breakdown products) will persist longer in ecosystems (watersheds or soils) with acidic pH. Recent monitoring data have shown that dicofol is sufficiently persistent to be transported via riverine input to the open sea and, in one study, to remote regions. Therefore it is concluded that dicofol is otherwise sufficiently persistent to justify its consideration within the scope of this Convention.

4. Reported log K_{OW} values for dicofol range from 3.5 to 6.06. The bioconcentration potential of dicofol in aquatic organisms is confirmed by experimental data. The reported bioconcentration factors (BCFs) in bluegill sunfish and common carp range between 6,100 and 10,000. If steady state is considered, the BCF in bluegill sunfish is 25,000. In a full life cycle test with the fathead minnow the highest observed BCF value was 43,000. The high BCF values are reflected by slow elimination from fish tissue with a half-life of 33 days. Model estimates indicate that dicofol can accumulate in aquatic species with modelled BCFs >5,000 L/kg ww. Partitioning coefficients between octanol/water and octanol/air, indicators of potential bioaccumulation in terrestrial animals for the screening assessment of POPs, show that bioaccumulation in terrestrial species might occur if metabolism is not considered. For mammals half-lives of approximately 14 days are reported.

5. Degradation products are considered in the hazard profile of dicofol. Major degradates of dicofol with a higher persistence than dicofol include DCBP (dichlorobenzophenone), FW-152 (2,2-dichloro-1,1-bis(4-chlorophenyl)ethanol), DCBH (dichlorobenzhydrol), OH-DCBP (3-hydroxy-dichlorobenzophenone) and DCBA (dichlorobenzilic acid). DCBP, FW-152 and DCBH accumulated in a water/sediment study and can be considered as persistent in sediment. US EPA (2009) suggested a half-life of 313 days in soils for p,p'-dicofol plus major degradates and 32 days for p,p'-dicofol alone under slightly alkaline conditions. Modelled log K_{OW} values for the metabolites are below the screening value of 5. In absence of experimental data the estimated bioconcentration potential for the metabolite FW-152 is high. The acute LC50 toxicity values of p,p'-DCBP and p,p'-FW-152 for rainbow trout are >2.29 mg/L and 0.24 mg/L indicating for p,p'-FW-152 high toxicity to fish. The metabolite p,p'-DCBP has been shown to reveal potent antiandrogen activity *in vitro*.

6. The potential of dicofol for long-range transport (LRT) has been confirmed by screening information from physical chemical information, estimated degradation half-lives in air, the application of LRT models and [monitoring information from remote areas]. Atmospheric oxidation by hydroxyl radicals (OH) is a possible removal pathway for dicofol in the atmosphere. Depending on the OH radical concentrations half-lives are between 3.1 to 4.7 days.

7. LRT model results show that dicofol can be transported to remote regions with moderate efficacy and that it has a high modelled capacity for enrichment in the Arctic environment. [Though monitoring information from remote areas is limited, transport via air and seawater to the high Arctic demonstrates that dicofol can be detected far from sources due to LRT.] No measurements from biota in remote regions were found in the literature. Among other reasons difficulties to analyse dicofol properly could be involved in this observation.

8. In most of the recent environmental monitoring studies dicofol is not directly measured but dicofol application is indicated by the ratio of measured DDT (o,p'-DDT/p,p'-DDT), leading to the conclusion that dicofol is one source for current DDT pollution at least in regions of dicofol use. However, use of isomer ratios to determine whether dicofol is the source of environmental loads of DDTs should take into account environmental fate characteristics of the isomers.

9. Dicofol is classified for environmental hazards according to the Globally Harmonized System as very toxic to aquatic life (H400) and as very toxic to aquatic life with long lasting effects (H410). The lowest observed acute (96h-LC_{50}) and chronic (95d-NOEC) effects for fish were 0.053 and 0.0044 mg/L, respectively.

10. Dicofol has shown reproductive effects such as eggshell-thinning and feminization of male embryos in birds. Dicofol, DCBP and FW-152 have been detected in bird eggs indicating maternal transfer to offspring. Dicofol has been detected in a variety of environmental compartments and biota. With regard to the reported chronic and acute laboratory derived effect concentrations of dicofol (e.g. $NOEC_{fish}$ 0.0044 mg/L), the detected environmental concentrations in biota (up to 3.9 mg/kg) in crop areas (US EPA 2009) and water bodies in areas of dicofol use (up to 0.0036 mg/L, Bishnu et al. 2009) may indicate the potential for causing adverse effects in wildlife on a local and regional scale.

11. The metabolism of dicofol has been studied in laboratory rodents. After uptake dicofol is distributed preferentially to adipose tissue but also to muscles, lung, testes, liver, kidney, brain and heart and is eliminated mainly in the faeces. It has been shown that dicofol retains to a greater extent in adipose tissue of female rodents. In humans dicofol or its degradation products have been detect in breast milk, blood, colostrum and adipose tissue in the low ng/g and ng/ml range. (Haraguchi et al. 2009, Lessenger & Riley, 1991, Wang et al. 2011, Lucardo et al. 2013b, Wang et al. 2014). The maximum concentration of 559 ng/g was detected in adipose tissue (Wang et al. 2011).

12. Dicofol exhibits moderate acute toxicity in mammals; common signs of toxicity include decreased spontaneous motor activity, ataxia, passiveness, somnolence, prostration, and occasionally tremors. Chronic toxic effects concern the liver, thyroid, adrenals, brain, heart and testes. A number of recent in vitro studies demonstrate interaction with the endocrine system, protein binding activity, enzyme induction and interference with other chemicals. There is some evidence of neurotoxicity, immune effects, and reproductive effects. The assessment of dicofol by IARC (1998) found that no overall evaluation of the mutagenicity of dicofol could be made; there is limited evidence that it is carcinogenic to experimental animals and insufficient data to evaluate the carcinogenicity of dicofol to humans. Recent epidemiological studies have shown that dicofol exposure is associated with a greater incidence of prostate cancer. Certain epidemiological studies have noted associations between dicofol exposure and prostate cancer in men and leukaemia, Hodgkins disease and autism disorders in children. Limitations of these studies hinder definitive causal relationships. These epidemiological studies illustrate the concern that adverse effects associated with dicofol exposure might also occur in humans. Risk assessment for consumers has clearly demonstrated exceeding acceptable exposure limits by orders of magnitude (EFSA 2011).

13. [Based on persistence, bioconcentration, high aquatic toxicity, widespread occurrence in environmental compartments, together with the *in vitro* evidence of endocrine related effects of dicofol it is concluded that dicofol is likely, as a result of its long-range environmental transport, to lead to significant adverse human health and environmental effects, such that global action is warranted.]

1. Introduction

14. In May, 2013 the European Community and its Member States submitted a proposal to list dicofol in Annex A, B and/or C of the Stockholm Convention (UNEP/POPS/POPRC.9/3), which was considered by the Persistent Organic Pollutants Review Committee (POPRC) at its ninth and tenth meetings held in October 2013 and 2014.

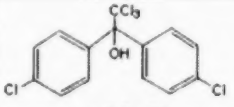
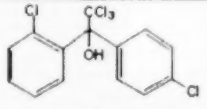
15. Dicofol is an organochlorine miticidal pesticide and acaricide and was introduced commercially in 1955 (WHO 1996). Dicofol acts as a mitochondrial electron transport inhibitor (Sanchez et al. 2010). The substance has been used primarily in East and Southeast Asia, the Mediterranean coast, as well as in Northern and Central America (Li et al. 2015). Intended uses of dicofol cover fruits, vegetables, ornamentals, field crops, cotton, Christmas tree plantations, and non-agricultural outdoor buildings and structures (US EPA 1998, Li et al. 2015). Concerning the mode of action in target organisms WHO (1996) reported that dicofol produces stimulation of axonal transmission of nerve signals, believed to be related to inhibition of ATPases in the central nervous system (CNS). The signs of toxicity are consistent with CNS depression. However, the Insecticide Resistance Action Committee (IRAC) has recently classified the mode of action for dicofol as

unknown or uncertain (IRAC 2008 cited in US EPA 2009). Sanchez et al. (2010) reported that dicofol acts as a mitochondrial electron transport inhibitor.

1.1 Chemical identity

16. Dicofol is comprised of two isomers: p,p'-dicofol and o,p'-dicofol. The technical product (95% pure) is a brown viscous oil and is composed of 80-85% p,p'-dicofol and 15-20% o,p'-dicofol with up to 18 reported impurities. The purer form is generally >95% dicofol which contains less than 0.1% DDT and related compounds (ΣDDT, i.e. DDT, DDE and DDD) (WHO 1996). Please see Table 1.1-1 for the chemical identity of dicofol.

Table 1.1-1. Chemical identity of dicofol

Common name IUPAC Chem. CAS chemical name	Dicofol 2,2,2-trichloro-1,1-bis(4-chlorophenyl)ethanol Benzenemethanol, 4-chloro-α-(4-chlorophenyl)-α-(trichloromethyl)- (CAS Registry)[1] 4-chloro-alpha-(4-chlorophenyl)-α-(trichloromethyl) benzene-methanol (WHO, 1996) 1,1-bis(4'-chlorophenyl)2,2,2-trichloroethanol (UNEP/POPS/POPRC.9/3)
Other names	1,1-bis(4-chlorophenyl)-2,2,2-trichloroethanol and 1-(2-chlorophenyl)-1-(4- chlorophenyl)-2,2,2-trichloroethanol ('p p'- and o,p'-isomer) (US EPA, 1998)
CAS registry number	115-32-2 (dicofol, p,p'-dicofol); 10606-46-9 (o,p'-dicofol
Trade name	1,1-bis(chlorophenyl)-2,2,2-trichloroethanol; 4-chloro-α-(4-chlorophenyl)-α-(trichloromethyl)-; Acarin; Benzenemethanol; Carbax; Cekudifol; CPCA; Decofol; Dicaron; Dichlorokelthane; Dicomite; Difol; DTMC; ENT 23648; FW293; Hilfol; Hilfol 18.5 EC; Kelthane; Kelthanethanol; Kelthane A; Kelthane (DOT); Kelthane Dust Base; Kelthane 35; Milbol; Mitigan; p,p-dicofol; NA2761 (DOT); NCI-C00486 (WHO, 1996).
Molecular formula	$C_{14}H_9Cl_5O$
Molecular weight	370.49
Structural formulas of the isomers	 p,p'-dicofol CAS No. 115-32-2  o,p'-dicofol CAS No. 10606-46-9

Physical and chemical properties

17. Dicofol has a water solubility around 1 mg/L and a low vapour pressure. The Henry's Law constant indicates low volatility from water and volatilization from moist soil surfaces is not expected to be an important fate process (HSDB 2015). However reported values differ considerably (cf. Table 1.1-2). Zhong et al. (2014) suggested that the low Henry's Law constant and the higher log Koa value of dicofol favour dicofol scavenging from atmosphere, and also dicofol partitioning in seawater. If released to air, a vapour pressure of 5.3×10^{-5} at 25 °C indicates that dicofol will exist in both the vapour and particulate phases in the atmosphere (HSDB 2015). Dicofol absorbs light >290 nm (HSDB 2015).

[1] http://www.cas.org/content/chemical-substances

Table 1.1-2. Selected physical and chemical properties

Property	Results	Source
Melting point, °C	77.5 78.5 - 79.5	Mackay et al. (2006) Tomlin (2001) in Rasenberg (2003)
Boiling point, °C	180 193 225	0.1 mmHg, Mackay et al. (2006) 360 mmHg, tech., Mackay et al. (2006) 665 Pa, UNEP/FAO/RC/CRC.2/14/Add.4
Density, g/cm³	1.45	Tomlin (1994) in Mackay et al. (2006)
Solubility in water, mg/L, at 25°C	0.8 1.32	Mackay et al. (2006) US EPA (2009)
Vapour Pressure, Pa, at 25°C	5.3×10^{-5} 2.5×10^{-4}	Mackay et al. (2006) PPDB (2012) in UNEP/POPS/POPRC.8/INF/13
Henry's Law Constant	5.66×10^{-5} Pa m³/mol (25°C) 2.45×10^{-2} Pa m³/mol (25°C) 1.44×10^{-7} atm m³/mol	Mackay et al. (2006) PPDB (2012) cited in UNEP/POPS/POPRC.8/INF/13, Saito et al. 1993 cited in Zhong et al. (2014) US EPA (1998)
Partition coefficient octanol/water (log Kow)	3.5 3.54 – 4.28 4.08 – 5.02 5.02 6.06	Kelly et al. (2007) Mackay et al. (2006) Rasenberg (2003) Li et al (2015, Supporting Information), measured value recommended by EPI SUITE TM US EPA (2009), measured value
Partition coefficient organic carbon/water (log Koc)	3.8	US EPA (2009)
Partition coefficient air/water (log Kaw)	-5.01	UNEP/POPS/POPRC.8/INF/13 (measured value recommended by EPI Suite v 4.0)
Partition coefficient air/octanol (log Koa)	8.9 9.3 10.03	Kelly et al. (2007) UNEP/POPS/POPRC.8/INF/13 (estimated value, EPI Suite v 4.0) Li et al (2015, Supporting Information)

Analytical method

18. The analysis of dicofol is affected by several difficulties, which have to be considered when evaluating the reliability of study results: it undergoes thermal breakdown during analysis, it can degrade to p,p'-dichlorobenzophenone (DCBP) and cannot be distinguished from other DCBP sources if only DCBP is detected and it degrades at high pH (EURL-SRM 2013). LC-MS/MS sensitivity for dicofol is very poor and the compound is thus typically analysed via GC (e.g. using ECD, MSD or MS/MS). GC-analysis, however, is very challenging due to the poor reproducibility of dicofol decomposition within the hot GC-inlet and the risk of complete decomposition. The most efficient way to eliminate all the above error-sources is the use of isotope-labelled dicofol (e.g. dicofol-D8) as internal standard (EURL-SRM 2013). Also the procedures of extraction and clean-up in which water and other solvents, as acetonitrile, are used can lead to degradation of dicofol (Spain, 2006). In most of the recent environmental monitoring studies dicofol is not directly measured but dicofol application is indicated by the ratio of measured DDT (o,p'-DDT/p,p'-DDT).

1.2 Conclusion of the Review Committee regarding Annex D information

19. The POPs Review Committee evaluated the proposal regarding dicofol (UNEP/POPS/POPRC.9/3) according to the requirements in Annex D of the Stockholm Convention at its ninth and tenth meeting in Rome. In Decision POPRC-10/3 the Committee reached the conclusion that dicofol fulfilled the screening criteria specified in Annex D. The Committee also decided to establish an ad-hoc working group to review the proposal further and prepare a draft risk profile in accordance with Annex E of the Convention

1.3 Data sources

20. The draft risk profile is based on the following data sources:

a) Proposal submitted by the European Community and its member States that are Parties to the Convention (UNEP/POPS/POPRC.9/3, UNEP/POPS/POPRC.7/INF/3), 2013.

b) Decision POPRC-10/3 of the POPs Review Committee, 2014.

c) Factsheet on dicofol, UNEP/POPS/POPRC.8/INF/13

[http://chm.pops.int/Convention/POPsReviewCommittee/POPRCMeetings/POPRC8/POPRC7WorkingDocuments/tabid/2801/Default.aspx, 2015-01-15]

d) Information submitted by Parties and observers according to Annex E of the Albania, Convention: China, Ecuador, Japan, Kenya, Mali, Netherlands, Serbia, Sweden, United States of America, International POPs Elimination Network (IPEN) and Pesticide Action Network (PAN)

This information is available on the Convention's website. [http://chm.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC10/POPRC10Followup/Dicofol(AnnexEinformation)/tabid/4293/Default.aspx, 2015-01-15].

e) International Programme on Chemical Safety, Dicofol, WHO/FAO Data Sheets on Pesticides No. 81 World Health Organization, Geneva, July 1996 [http://www.inchem.org/documents/pds/pds/pest81_e.htm, 2015-01-15]

f) Ospar Commission, 2002. Hazardous Substances Series, Dicofol. [http://www.ospar.org/v_publications/download.asp?v1=p00150, 2015-01-15]

g) US EPA, 1998. Reregistration Eligibility Decision (RED), Dicofol [http://envirocancer.cornell.edu/turf/pdf/dicofol_red.pdf, 2015-01-15]

h) US EPA, 2009. Risks of Dicofol Use to Federally Threatened California Red-legged Frog (*Rana aurora draytonii*) [http://www.epa.gov/espp/litstatus/effects/redleg-frog/dicofol/analysis.pdf, 2015-01-15]

In addition to these information sources, a literature search of public data bases was conducted that focused on recent scientific literature. The following databases were included: ECOTOXicology database, EU plant protection database, EFSA pesticides database, Pubmed, SYRAUSE Environmental Fate DataBase, OECD eChemPortal, TOXNET, The Carcinogenic Potency Database, NITE DataBase, GESTIS, WHOLIS Library and information networks for knowledge database, WHO, IPCS Inchem (International Programme of Chemical Safety), Biocatalysis/Biodegradation databases, PAN pesticide database, Google scientific search, U:search (University search, all e-journals).

1.4 Status of the chemical under international conventions

21. Dicofol is subject to a limited number of international treaties and conventions:

a) In December 2009 dicofol was proposed to be added to Annex I (prohibition of production and use) of the Aarhus Protocol on Persistent Organic Pollutants (POPs) under the Convention on Long-Range Transboundary Air Pollution. The POPs Task Force (except for one expert) concluded that Dicofol met the indicative numerical values of the Executive Body decision 1998/2. However no finalized action for dicofol under the LRTAP POPs Protocol was taken pending further consideration under the Stockholm Convention. In December 2013, the Executive Body of LRTAP decided to defer any discussion of dicofol until after COP7 of the Stockholm Convention in 2015[2] (Annex E information 2015 from USA).

b) The OSPAR Commission included dicofol in the List of Chemicals for Priority Action (by 2004). Further information can be found at http://www.ospar.org/

c) In 2012 the Chemical Review Committee (CRC) of the Rotterdam Convention on the Prior Informed Consent Procedure (PIC) for Certain Hazardous Chemicals and Pesticides in International Trade decided that for dicofol a notification from another PIC region is outstanding, therefore at this time dicofol has not been recommended for listing in Annex III of the Convention.

d) Since 2009 the specific exemptions for DDT (dichlorodiphenyltrichloroethane) listed in Annex B of the Stockholm Convention as intermediate in the production process of dicofol is outdated and no new registrations may be made with respect to such exemptions. However, use of DDT as a closed-system site-limited intermediate that is chemically transformed in the manufacture of other chemicals that, taking into consideration the criteria in paragraph 1 of Annex D, do not exhibit the characteristics of persistent organic pollutants is still allowed upon notification to the Secretariat (subject to a time limitation and a 5 yearly review for registered members).

2. Summary information relevant to the risk profile

2.1 Sources

2.1.1 Production, trade, stockpiles

22. Dicofol has been manufactured from technical DDT by hydroxylation of DDT (van de Plassche et al. 2003). In several countries regulations exist with respect to the ΣDDT content of commercial dicofol. The FAO Specification 123/TC/S/F (1992) requires ΣDDT to be less than 0.1%.

[2] http://www.unece.org/fileadmin/DAM/env/documents/2013/air/eb/ECE_EB.AIR_122_E.pdf

In Australia, Brazil, Canada, Japan, EU, and USA the limit is 0.1% (van de Plassche et al. 2003). Qiu et al. (2005) mentioned the legal requirement in China for DDT impurity to be no more than 0.5% of technical dicofol or no more than 0.1% of formulated dicofol by 2003. However, dicofol productions with impurities of ΣDDT above these standards are still available on the Chinese market even after that date. The authors reported an average contents of o,p'-DDT, p,p'-Cl-DDT, o,p'-DDE, and p,p'-DDT in 23 commercially available dicofol formulations of 11.4, 6.9, 4.4, and 1.7 %, respectively. This equals a ΣDDT content of 24.4%. Also Turgut (2009) investigated dicofol formulations on the Turkish market. The ΣDDT content of formulated dicofol was between 0.3% and 14.3%. A content of 3.5% ΣDDT has been reported in dicofol produced in India (van de Plassche et al. 2003).

23. Global production of dicofol between the year 2000 and 2007 was estimated to be 5,500 t/y (tonnes/year), whereas production in USA was estimated at 160 t/y for the years 1999 to 2004 (Hoferkamp et al. 2010). Spain produced approximately 1500 t/y (formulating was conducted in Italy), and use was reported to be 100–150 t in 2000 (van de Plassche et al. 2003). Until 2006 Spain was the major manufacturer and consumer (90 t in 2006) of dicofol in Europe (OSPAR, 2008).

24. The following notifications were made to the Stockholm Convention's register for closed site limited production/uses (UNEP, 2015[3]). In Brazil, dicofol was produced by Nortox (plant capacity was 200 kg/d), but production ceased in 2003 and 2004 for closed-site limited production. In India production and use was on the date of notification (10/27/2006) 150 t. Dicofol was produced in a closed system in batches. On the basis of the notification submitted to the Secretariat by India on 10 March 2014, the production and use of DDT as a closed-system site-limited intermediate in the production of dicofol has been extended until 15 May 2024 (UNEP/POPS/COP.7/4/Rev.1). In China production and use were on the date of notification (2/2/2005) 3,000-4,000 t. About 80% of DDT was used as an intermediate in the production of dicofol. There were 6 enterprises with the capability to produce dicofol (UNEP, 2015).

25. China has been a major producer of technical DDT and dicofol, with >85% of the global technical DDT production occurring here, which amounted to approximately 97,000 t between 1988 and 2002. Over half of this amount (approximately 54,000 t) was used to manufacture dicofol (40,000 t) (Qiu et al. 2005). In China, the enterprises registered to produce technical dicofol and its formulations were distributed in 13 provinces and municipalities. Currently, there is only one technical dicofol producer in China (Annex E information, China, 2015). In 2013, this producer stopped producing technical dicofol. In 2014, it shut down its production line for technical dicofol. By a letter dated 28 February 2014, China notified the Secretariat that as of May 2014 it had withdrawn the use of DDT as a closed-system site-limited intermediate starting from June 2014 (UNEP/POPS/COP.7/4/Rev.1-Corr.1).

26. In India, the Indian state-owned enterprise, Hindustan Insecticides Ltd, has a production capacity for dicofol of 150 t/y (company homepage[4]) and still manufactures dicofol with an average annual production output of approximately 50 t (Li et al. 2015). No data on current production could be found in literature regarding other potential current producers, e.g. Dow AgroSciences and Adama Agricultural Solutions Ltd (formerly Makhteshim Agan Industries Ltd)

27. In 2011 US EPA published an order for the voluntary cancellation of dicofol at the request of the registrant (Makhteshim Agan of North America, Inc). Existing stocks provision allowed the registrant to reformulate it into end-use products and sell it until 2013. Sale and distribution by others was allowed until 2013. A final rule revoking most dicofol residue tolerances was issued in 2012. Import tolerances for tea were maintained pending future decision making (Annex E information, USA, 2015).

2.1.2 Uses

28. Dicofol is used as miticidal pesticide and acaricide in many countries around the world and reported to be applied to food, feed, and cash crops including apple, citrus, lichi, longan, pear, leafy vegetables, tea, and cotton (Li et al. 2015). It is also used on ornamentals such as orchids. In Senegal, dicofol is used on onion, watermelon, potato and pimento crops (Jepson et al. 2014). In Mexico, there are 17 registrations for dicofol, which is authorized for the application on aubergine, chilli, strawberry, lime, apple, orange, pear, watermelon, mandarin, grapefruit, vine, citrus fruits, ornamental shrubs, ornamental plants and nursery gardens (comment from Mexico, May 2015, to the POPRC dicofol draft risk profile). In China, dicofol is not permitted on vegetables or fruit (Wang et al. 2015). It is reported to be restricted or prohibited in most developed countries. In Canada use has not been permitted since

[3] http://chm.pops.int/Implementation/Exemptions/RegisterofSpecificExemptions/tabid/1133/

[4] http://www.hil.gov.in/DICOFOL%20.html

2011 and in USA will not be after 2016 (Li et al. 2015; Annex E information, USA, 2015). Dicofol is banned in Benin, Côte d'Ivoire, the European Union, Guinea, Iraq, Japan, Mauritania, Oman, Romania, Saudi Arabia, and Switzerland (Annex E information, 2015 and comments from Iraq and Côte d'Ivoire, May 2015, to the POPRC dicofol draft risk profile).

29. Li et al. (2015) estimated, based on a combination of literature surveys, field surveys and personal communications, a total of 28,200 t (tonnes) of dicofol used globally in a 13 year period from 2000 to 2012, mainly in Asia (21,719 t), followed by North America (1,817 t), Europe (1,745 t), Latin America (1,538), Africa (1,434 t) and Oceania (13 t) The estimated use by continent in 2012 was for Asia 619 t (mainly in China 530 t and India 43 t), North America (USA) 33 t, Latin America 38 t, Africa 36 t, and Oceania around 1 t. Over the period 2000 to 2012, 76.8% of the usage was estimated in Asia and there mainly in China (69.1% of total usage). However, between 2000 and 2012 the estimated dicofol usage decreased by 75% in China (from 2,013 t to 530 t), 69% in India (from 145 t to 43 t) and 90% in the USA (from 324 t to 33 t) with most use occurring in California and Florida. The decrease of estimated global use from 2000 (3,350 t) to 2012 (730 t) was approximately 80%. Average application rates were 1.3 kg/ha, 0.44 kg/ha and 0.31-0.45 kg/ha in the USA, Europe and China, respectively (Li et al. 2015).

30. In Europe dicofol usage decreased from 317 t to 32 t between 2000 and 2009. According to estimated emission data published by van der Gon et al. (2007), the major consuming countries in 2000 were Spain, Italy, Turkey, Romania, and France. In EU countries, the use of dicofol for plant protection products expired by 2010 at the latest according to Commission Decision 2008/764/EC[5]. In addition all non-agricultural uses are prohibited according to the Biocidal Products Regulation No (EC) 528/2012[6].

31. Notice No. 11 of 1997 issued by Ministry of Agriculture of China banned the use of dicofol on tea plants. Ministerial Announcement of Agriculture No. 199 of 2002 restressed the ban of dicofol on tea plants. At present, registered use of dicofol in China is to prevent *Tetranychus cinnbarinus*, *Tetranychus viennensis (Zacher)* and *Phyllocoptruta oleivora (Ashmead)* on cotton, citrus and apple trees (Annex E information, China). The market share of dicofol in China's acaricide market has declined from 27% (in 1999) to less than 8% after 2008 (Li et al. 2015).

32. In summary the data provided by Li et al. (2015), together with other above mentioned literature sources, plausibly indicate a decreasing trend of global dicofol usage, which probably is continued after the observed study period (2000-2012). Therefore, it can be estimated, that the current global dicofol use is well below 1,000 t/y.

2.1.3 Releases to the environment

33. Principal releases to the environment can occur from the production process, professional or private use and the resulting waste. Li et al. (2015) estimated via BETR-Global Modelling the realistic global contribution of dicofol and concluded that, of the estimated 28,200 t used between 2000 and 2012, 731 t remain in the environment. They also estimated that 1.9 t of dicofol has been deposited in the Arctic, and 2.2 t in the Antarctic as a result of LRT.

34. Dicofol is produced in a closed system but releases can result from improper production practices. Li et al. (2014) described DDT, dioxin and furan releases from a closed system dicofol production process in China. The annual amounts of ΣDDT and p,p'-DDT directly released to the environment via the use of dicofol were estimated as 9,480 kg and 1,080 kg, respectively. From the PCDD/F distribution patterns, it is suggested that the major pathway for PCDD/F formation involves precursor synthesis during the production of dicofol in the closed-system process, which is estimated to result in an annual release to the environment of 0.17 g I-TEQ (toxicity equivalent value) from this particular company (Li et al. 2014).

2.2 Environmental fate

2.2.1 Persistence

Abiotic degradation

35. Both dicofol isomers are susceptible to aqueous hydrolysis and the hydrolysis degradation rate is pH dependant. o,p'-Dicofol hydrolysed with half-lives of 47 days at pH 5, 8 hours at pH 7, and 9 minutes at pH 9. p,p'-Dicofol hydrolysed with half-lives of 85 days at pH 5, 64 hours at pH 7, and 26 minutes at pH 9 at 25°C (IUCLID cited in Rasenberg, 2003; US EPA 1998). The major degradate in the studies, the o,p'- and p,p'-isomer of dichlorobenzophenone (DCBP), appeared to resist further

[5] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32008D0764

[6] http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=OJ:L:2012:167:TOC

degradation (no quantification was provided in US EPA, 1998). Other metabolites for p,p'-dicofol were isolated but not identified (US EPA 1998). According to Boethling et al. (2009) the potential for the formation of more persistent degradation products must also be assessed for all POPs.

36. At a pH of 5, the half-life of dicofol's main p,p'-isomer was 85 days, fulfilling the cut-off value of 60 days for persistence in water (UNEP/POPS/POPRC.10/10). Approximately 680 (14%) out of 4,837 watersheds i.e. lakes and rivers from northern European countries (DK, GB, IE, FI, NO, SE, EE) have a minimum pH value of ≤6 and 139 (3%) watersheds displayed a pH ≤5. The data were extracted from the European Environment Agency (2015) Waterbase databank[7]. Pienitz et al. (2004), Hawes et al. (2002) and Michelutti et al. (2002) reported in addition to neutral and alkaline pH values also acidic pH values in several Arctic lakes and ponds. Black-water rivers found in several areas around the world (Australia, Amazonia, Europe, Indonesia, the Orinoco basin and the northern and southern areas of the United States) typically have a pH of around 5 (Alkhatib and Jennerjahn 2007).

37. Experimental data on aqueous photolysis of dicofol at pH 5 showed that o,p'-dicofol photolysis with a DT50 of 14.8 days and p,p'-dicofol photodegraded with a half-life of 92.5 days (US EPA, 1998). If corrected for the control samples the DT50 values for o,p'-dicofol and p,p'dicofol are 27.5 and 244 days, respectively (US EPA, 2009). US EPA (2009) reported soil photolysis half-lives of 56 and 21 days for o,p and p,p'-dicofol, respectively. Photolytic half-lives of 30 days for both isomers were cited in Spain (2006). However the photolysis studies lacked information with regard to the light spectrum and TLC chromatograms. p,p'-DDD and DCBH were detected with 4.5% and 20% applied radioactivity respectively (Spain, 2006). US EPA (2009) concluded that photodegradation is not expected to be significant route of dissipation of dicofol in the environment.

38. The estimated atmospheric half-life for dicofol based on reaction with hydroxyl (OH) radicals is 3.1 days, using the default atmospheric hydroxyl radical concentration of 1.5×10^6 molecules/cm^3 during sunlight hours in AOPWIN, EPISUITE v4.11TM computer program[8]. Using a lower hydroxyl radical concentration of 5×10^5 molecules/cm^3, which is generally used as a daily (24-hour) average in relatively unpolluted air in the EU (EC 2003), the atmospheric half-live is 4.7 days. It should be noted that hydroxyl radical reaction rates vary spatially and temporally with average daily sunlight, and 5×10^5 molecules/cm^3 may not be typical of northern latitudes since hydroxyl radical concentrations decline with latitude. Moreover AOPWIN estimates the gas-phase reaction rate for the reaction between OH radicals and the chemical at 25°C. However based on the physical chemical properties (cf section 1.1) dicofol can exist in air in the gas and particulate phase. (HSDB, 2015) reported for dicofol light absorption at wavelengths >290 nm which suggests that photolysis may be an important degradation process in the atmosphere (Chen et al. 1984 cited in HSDB, 2015). Rena et al. (2011) studied the theoretical photodegradation mechanisms of dicofol by density functional theory calculations. The authors found that OH radicals attacking the C7-C8 bond and the addition of OH to the C12 atom of dicofol are favourable pathways. Besides one dominant reaction product $(C_6H_4Cl)_2CO$ a precursor for forming polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs), C_6H_4ClOH(4-CP) was identified.

Biotic degradation

39. In a ready biodegradability test, conducted according to the OECD 301C Test Guideline dicofol (at a concentration of 100 mg/L which is above the water solubility of 1 mg/L), reached 0% of its theoretical BOD (biological oxygen demand) in 4 weeks using an activated sludge inoculum at 30 mg/L (Japanese NITE database, 2015)[9].

40. The fate and behaviour of dicofol during wastewater treatment has been assessed by Oliveira et al. (2012). The authors specifically investigated the biodegradation of dicofol during aerobic wastewater treatment and anaerobic sludge biodigestion using ^{14}C labelled dicofol. Residues of dicofol, and the breakdown product DCBP, were quantified, but the recovery rate for dicofol in wastewater was only about 60%. After seven days of the aerobic process 55%-60% of the applied radioactivity (AR) was associated with the activated sludge (14% dicofol, 41% 'p,p'-DCBP and 45% to the wastewater (5% AR dicofol, 40% AR unknown metabolites). After aerobic treatment only 0.1% AR of dicofol was mineralised. After 18 days in the anaerobic process, only 3% of the dicofol and 5% of p,p'-DCBP was detected in the sludge with 70% of remaining radioactivity in the sludge associated with other metabolites. This study, therefore, suggests that dicofol can be degraded (in the system studied) to other compounds, but not mineralised. However, sewage treatment plants are not

[7] http://www.eea.europa.eu/data-and-maps/data/waterbase-rivers-10

[8] http://www.epa.gov/opptintr/exposure/pubs/episuite.htm

[9] http://www.safe.nite.go.jp/jcheck/detail.action?request_locale=en&cno=115-32-2&mno=4-0226 (Reports: Dicofol (The results of the investigation))

expected to be primary receiving compartments for dicofol; this route of elimination may not be the most relevant to the use-profile for dicofol.

41. In a laboratory water/sediment test with two different water/sediment systems (pH >7) DT50 values in the whole sediment/water system were between 7 and 13 hours for p,p'-dicofol and less than 2 hours for o,p'-dicofol. Isomer specific accumulation in sediments of major metabolites at the end of the experiment after 100 days occurred for p,p'-DCBP (22% AR), p,p'-DCBA (dichlorobenzilic acid, 10% AR) and o,p'-DCBH (dichlorobenzhydrol, 40% AR). Other major metabolites >10% AR detected in the studies were: o,p'-DCBP, p,p'-DCBH, p,p'-FW-152 (2,2-dichloro-1,1-bis (4-chlorophenyl)ethanol) and o,p-DCBA (UNEP/POPS/POPRC.8/INF/13, Spain, 2006). A new study with water/sediments at pH <7 has been required for the assessment of the fate of dicofol in the aquatic environment (Spain, 2006 in UNEP/POPS/POPRC.8/INF/13). Rasenberg (2003) indicated half-lives in sediment for DCBP, DCBH and DCBA in the range of 7 to 13 days, 197 to 429 days and 24 to 174 days, respectively. However no study details or study source has been quoted. According to Annex E submission (2015) from USA, dicofol is expected to partition to sediment based on log Kow of 6.06 and a Koc of 7,060 mL/g. US EPA (2009) stated that anaerobic soil metabolism studies (pH value 7.9) indicate that dicofol will degrade relatively rapidly in sediment with a half-life less than 30 days. Xia (2008) reported enhanced disappearance of dicofol by water hyacinth in a laboratory study.

42. In an aerobic soil study under laboratory conditions (20-25°C), o,p'-dicofol was degraded more rapidly than p, p'-dicofol. The data showed that the rate of degradation was fastest in soils with higher pH. Reported DT50 values in the two soils (pH >7) ranged from 9 to 204 days for the two isomers. In the other two European soils (pH <7), no degradation was observed under the study conditions. Mineralisation was low (Spain, 2006 cited in UNEP/POPS/POPRC.8/INF/13). According to the results of degradation studies in soil and the results of the hydrolysis studies, the degradation of dicofol is pH dependant (Spain, 2006). Many areas especially in northern Europe have a soil pH<7 (Böhner et al. 2008). pH in soils globally can be found in IGBP-DIS (1998). In the Annex E submission (2015) from Sweden referring to an ecotoxicological evaluation in 1988, it was concluded that dicofol has a slow degradation.

43. US EPA (2009) indicated for lab soil simulation studies that o,p'-dicofol degraded with a half-life of 8.5 days in a loam soil and the p,p'-isomer degraded with a half-life of 32 days in a silt loam soil. Major metabolites for the p,p'-isomer were p,p'-FW-152, p,p'-DCBP, and 3-hydroxy-4, 4'-dichlorobenzophenone (3-OH-p,p'-DCBP). Volatile residues were 21-22% and <4% of the applied and unextractable residues were 10-15% and 57-61% of the applied after 12 months for the p,p'- and o,p'-dicofol isomer, respectivley (US EPA 1998). Parent plus major degradation products of concern (including the o,p'- and p,p'-isomers of DCBP, FW-152, DCBH, OH-DCBP) degraded with a half-life of 104.5 days and 313 days in two soil metabolism studies for o,p'-dicofol and p,p'-dicofol, respectively (US EPA 2009).

44. US EPA (1998) stated that in ecological monitoring studies conducted in Florida and California, dicofol dissipated from the soil surface with a half-life ranging from 58 to 113 days. In a dissipation study on cotton in California half of dicofol residues dissipated in less than 7 days. In another dissipation study on strawberries in California dissipation DT50s of 22 days for o,p'-dicofol and 72 days for p,p'-dicofol were measured. Kumari and Duhan (2011) carried out a field trial in India to assess the persistence of residues of dicofol on cotton and in soil after spraying. Residues dissipated almost completely from soil in 60 days (dissipation half-life of 9 days). However the soil was extracted with ammonia and the detection method did not account for analytical losses. Dicofol residues were detected in cotton lint and seed. No degradation products were measured or suggested by the authors. A field trial at 26°C and pH 5.9 reported a (dissipation) half-life of 40 to 50 days (study author Hofmann 1986 Annex E information, 2015, Sweden). However no DT50 value could be calculated from this study according to Spain (2006). EFSA (2014) pointed out that there are a number of difficulties in the determination of a reliable degradation rate parameter from field studies e.g. the initial decline of applied substance can be more rapid followed by a slower rate of decline, loss of the substance due to volatilisation or leaching, uptake by plants, run-off etc. However, translocation processes did not play a part in the loss or degradation rate of dicofol in the Florida and California studies.

45. US EPA (2009) indicated a conservative estimate for persistence of dicofol (considering the parent and major degradates) of as high as 313 days and noted the lack of adequate information to estimate persistence of dicofol degradates in the environment. Based on the available environmental fate data, US EPA determined that dicofol is not expected to persist in the environment, with half-lives less than 90 days in soil, depending upon the specific environmental conditions.

Monitoring data

46. Weaver et al. (2012) investigated organochlorine residues in surface soils from the Namoi Valley, Australia. The study aimed to quantify historical residues in soils. Dicofol was measured and detected by a certified Government analytical laboratory in one Vertisol soil sample at 18 ng/g. The pH of this soil was 6.9 ($CaCl_2$) and the detected level was attributed to a historic use (T. Weaver, personal communication, March, 2015). Dicofol was also measured in deeper layers in dated sediment cores from lake Saint André in northern France by Sabatier and co-workers. Measured residues traced back to the 1940s with highest levels in the 1970s, 1992, and 2000. Though no half-lives were calculated the data indicate that dicofol can persistent in this environment for several decades (Sabatier et al. 2014). Zhong et al. (2014) measured high dicofol levels in surface sediment samples from the coastal and offshore regions of the Bohai and Yellow seas. The presence of concentrations of dicofol at river estuaries, sea water (pH >7) and sea sediments suggests that dicofol is sufficiently persistent to be distributed to the sea. Mean concentrations of dicofol near the Yangtze River and Yellow River estuaries were seven times higher than those at other sampling sites (Zhong et al. 2014) indicating higher inputs closer to the estuaries. Though data for remote regions are very limited, dicofol has been detected in the Arctic environment in seawater and air (one study: Zhong et al. 2012) suggesting sufficient persistence to be transported to higher latitudes (reported levels from source regions and higher latitudes are reported in section 2.3.1).

Summary on persistency

47. Experimental evidence suggests that abiotic as well as biotic degradation of dicofol are dependant on the pH value of the receiving environmental compartment with longer degradation half-lives under acidic conditions. o,p'-Dicofol and p,p'-dicofol are stable under acidic conditions in hydrolyses studies. According to the available laboratory studies dicofol will degrade in aquatic compartments with a pH >7. Experimental primary degradation half-lives for dicofol in soil are equivocal, but according to field studies (California and Florida) dicofol is not persistent in soils. However no field studies in colder climates are available. A conservative estimate for persistence of o,p'- and p,p'-dicofol (considering the parent and major degradates of concern) of as high as 104.5 and 313 days in soil (from laboratory studies) was reported. Recent monitoring data have shown that dicofol is sufficiently persistent to be transported via riverine input to the open sea and to be detected in deep sediment layers dated back to 1940s. One study has measured dicofol in remote regions. Modelled data indicate that the persistence of dicofol in the environment is lower or comparable to benchmark substances and known POPs.

2.2.2 Bioaccumulation

Screening assessment based on physical-chemical properties

48. The reported log Kow values for the p,p'- and o,p'-isomers of dicofol span a wide range from 3.5 to 6.6, respectively (see section 1.1). A maximum measured log Kow value of 6.06 was used for modelling estimates by US EPA (2009). The following log Kow values for dicofol are reported by Li et al. (2015): 5.02 (measured value recommend by KOWWIN in EPI suite), 4.18 (logarithmic mean of measured values 4.08-4.28) for p,p'-dicofol and 4.40 (logarithmic mean of measured values 4.32-4.34) for o,p'-dicofol. For dicofol metabolites (DCBP, FW-152, DCBH and OH-DCBP), estimated log Kow values ranging from 3.96 to 4.89 (EPISuite v.4.0) are cited in US EPA (2009). These values indicate a potential for bioconcentration in aquatic organisms for dicofol as well as for its degradation products, although most of them are below the screening trigger of 5 of the Stockholm Convention.

49. The octanol/air partition coefficient (Koa) is mentioned as an indicator of potential bioaccumulation in terrestrial animals for the screening assessment of POPs (UNEP/POPS/POPRC.3/INF/8, 2007). Kelly et al. (2007) proposed that the biomagnification of dicofol in the terrestrial food chain is particularly relevant, because it has a high log Koa. The proposed log Koa values for dicofol are between 8.9 and 10.03 (Kelly et al. 2007; Li et al., 2015, Supporting Information), respectively. Based on a log Kow range of 3.5 to 6.06 and a log Koa range of 8.9 to 10.02, a high bioaccumulation potential in both air-breathing organisms and aquatic organisms can be expected (log Kow higher than 2 and a log Koa higher than 5 according to ECHA 2008). For the degradation products log Koa values were estimated with KOAWIN EPISuite v.4.1. Estimated log Koa values were 8.799 for DCBP, 12.07 for FW-152, and 10.4 for DCBH. Log Kow values und log Koa values for the metabolites are in the range that indicate a high bioaccumulation potential in terrestrial organism according to Kelly et al. (2007) and ECHA (2008).

Bioconcentration and bioaccumulation studies in aquatic organisms

50. In a 28-day laboratory BCF study with bluegill sunfish (*Lepomis macrochirus*) exposed to p,p'-dicofol, a BCF of 10,000 was observed in whole fish (steady state was not reached), the estimated steady-state BCF for dicofol was 25,000 US EPA (2009). In this study, parent dicofol represented >94% of the radioactivity measured after the 28-day exposure, suggesting that metabolism of dicofol was minimal in fish. FW-152 and OH-DCBH were detected in tissue samples (each at 4.7% AR) according to US EPA (2009) and UNEP/FAO/RC/CRC.2/14/Add.4 in Annex E information, Netherlands (2015).

51. UNEP/POPS/POPRC.8/INF/13 cited the same BCF of 25,000 for dicofol (p,p'-isomer) in fish with a slow clearance time and a estimated depuration rate (CT_{50}) of 110 days. No further information is given on the fish species used or BCF calculation details.

52. In an early life stage test with the aquatic invertebrate, *Hyalella azteca* and the fathead minnow (*Pimephales promelas*), mean 28-day BCF values of 10,000 (±3000) and 3,700 (±800), respectively, were observed. As the duration of this study was insufficient to allow the test organisms to reach steady-state, it is expected that if the duration had been extended, observed BCF values would have increased, according to US EPA (2009). In another study quoted in US EPA (2009), a full life cycle test (flow-through conditions) with the fathead minnow, the highest observed BCF value was 43,000, which was observed in F_0 females after 296 days of exposure to dicofol. The BCFs (based on total ^{14}C activity; range of 11,000 to 43,000) from this study indicated that dicofol tends to concentrate in the tissues of fish at all growth stages (Spain, 2006).

53. Studies according to the OECD 305 Test Guideline resulted in BCF values of 8,200 and 6,100, obtained for common carp exposed to 0.1 and 1 µg/L (Japanese NITE database, 2015[10]). A recent bioaccumulation test based on the use of zebrafish eleutheroembryos as an alternative to adult-individuals indicate that the BCF was highest for dicofol compared to chlorpyrifos and atrazine. Zebrafish eleutheroembryos (72 h after hatch) were exposed to 0.1 and 1 µg/L dicofol for a period of 48 hours. Steady state was not reached. The log BCF was 3.9 (=7,943 L/kg) calculated with two toxicokinetic models assuming steady state (El-Amrani et al. 2012). Based on analytical challenges to measure dicofol accumulated residues might also include breakdown products in the above cited studies.

Toxicokinetic and metabolism studies

54. In bluegill sunfish elimination was slow with minimal metabolism. The estimated depuration half-life was 33 days (US EPA 1998, US EPA 2009). Several toxicokinetic studies on rats and mice indicate a gender specific elimination rate with half-lives less than 8 days for single exposure. In an ADME (adsorption, distribution, metabolism, excretion) study in rats dicofol distributed preferentially to adipose tissue and was eliminated mainly in the faeces. Essentially the entire dicofol dose was excreted within 8 days (IPCS Inchem 1992). For repeated exposure elimination half-lives were estimated to be 6-14 days for dicofol (Steigerwalt et al. 1984b cited in IPCS Inchem 1992).

Assessment of bioconcentration and biomagnification models and monitoring data

55. Based on governmental assessment reports (US EPA 1998, US EPA 2009, Spain 2006) and the conducted literature search no empirical information on bioaccumulation, biomagnification and trophic magnification in food webs is available for dicofol.

56. However, Malik et al. (2011) examined the potential persistence and bioaccumulation for dicofol across three heronries based on the rivers Chenab, Ravi and the Rawal Lake Reservoir in the Punjab region of Pakistan. Samples of surface sediment (n=15, to a depth of 3-8 cm) along with prey item (e.g. insects, toads, fishes) (n=150) and egret eggs (n=30, one egg from each nest) from within the heronries were collected during the summer months of 2007. Sediment mean concentration from Chenab and Ravi were 12.5±18.4 and 11.3±16.2 ng/g, respectively. The key finding his that, in all cases, the greatest concentrations of dicofol from the three locations were found within egg samples (10±21.3, 38.4±50.2 and 48.3±53.3 ng/g, mean values) compared to prey (not detected, 21.6±30.6 ng/g and 10.3±14.5 ng/g, mean values), suggesting biomagnification in all three heronries. However results were not lipid corrected, so the values may not fully explain if there was in fact accumulation.

[10] http://www.safe.nite.go.jp/jcheck/detail.action?request_locale=en&cno=115-32-2&mno=4-0226 (Reports Dicofol (The results of the investigation))

57. Estimated BCF values for dicofol with the KABAM model[11] ranged from about 28,000 L/kg for filter feeders to about 55,000 L/kg for phytoplankton (USA, Annex E submission, 2015). Estimates of FW-152 residues in fish were highest among the model results for metabolites (US EPA 2009).

58. QSAR (Quantitative Structure Activity Relationship) estimates for the log BCF values of the metabolites p,p'-DCBP, p,p'-DCBP, p,p'-FW-152, o,p'-FW-152 and p,p'-DCBH, p,p'-DCBH was calculated using VEGA[12]. VEGA is an open source platform, that contains three BCF tools including one read across model. Read across, in this case, means that unknown values (in this case log BCF) of a target compound(s) are estimated based on the known values for structurally related substances. For FW-152 isomers a log BCF of 3.77 (5,904 L/kg) was calculated with the BCF read across model.

59. Kelly et al. (2007) calculated (assuming a log Kow of 3.5) high biomagnification factors (BMFs) in terrestrial species ranging from 6.1 in reptiles to 76 in humans. However, metabolic transformation can reduce or eliminate the anticipated biomagnification potential, but only if the metabolic transformation rate is sufficiently high, in which cases, the bioaccumulating behaviour of resulting metabolites should also be consider.

Summary on bioaccumulation

60. Dicofol has a high bioconcentration potential as demonstrated by experimental derived BCF values in fish that range from 6,100 to 43,000 and an experimental calculated depuration half-life of 33 days in bluegill sunfish. Model calculation indicates high biomagnification factors for terrestrial species, if metabolic transformation was not considered. For dicofol metabolites log Kow values are below 5, however log Koa values indicate that a high bioaccumulation potential might occur based on this screening information (without the consideration of metabolism). In addition a QSAR model calculation identified a high bioconcentration potential for FW-152.

2.2.3 Potential for long-range environmental transport

Screening of physical-chemical properties

61. Under Annex D, an atmospheric half-life >2 days is recognized as a criterion for long-range transport potential (LRTP). Calculated half-lives in air at 25°C in the gas phase for dicofol are between 3.1 and 4.7 days (cf. section 2.2.1). Taking into account the much lower temperatures of the troposphere, the half-life of dicofol under real situations is likely to be longer. The degradation rate constant is temperature dependant (cf. Aktinson 1989). Based on the vapour pressure combined with the propensity of the compound to sorb to particles (see section 1.1), dicofol is expected to partition between the gas and particle phases in the atmosphere. The average half-life time for particles is estimated to be about 3.5 - 10 days and the average life time for particles is estimated to be about 5 - 15 days (Atkinson et al. cited in Rasenberg 2003).

LRT model predictions

62. Several models have been developed for estimating the LRT potential of POP candidates. The MSCE (Meteorological Synthesizing Centre East) POP model (Vulykh et al. 2005), a multicompartment chemistry transport model, uses a benchmark approach to overcome model dependency of numerical values. Benzo(a)pyrene (B[a]P) is a listed POP in the UN ECE POPs Protocol and was selected as a benchmark substance because of its high travel distance of approximately 2,400 km, its environmental half-life of approximately 75 days. For their model, they assume dicofol half-lives of 3, 30 and 60 days in air, water and soil, respectively. The model predicts an atmospheric travel distance (TD; the distance after which the concentration has fallen beneath 1/1000 of that at the source) of 1,650 km. The estimated environmental half life of dicofol was 20 days. The ranking of dicofol and B[a]P with respect to environmental half life shows that dicofol is less persistent than B[a]P. According to the model calculations of TD, LRT of dicofol is slightly less than that of B[a]P.

63. US EPA (2009) estimated the overall persistence (Pov) and LRTP of dicofol and its breakdown products with the OECD "Pov and LRTP Screening Tool". Pov metrics combines estimates of single-media half-lives with the multi-media partitioning of a chemical and do not rely on the single-media half-lives as persistence criteria. Pov takes into account the environmental media a chemical is likely to partition to, and weigh the single-media half-lives with the chemical's fractions in the individual media (Wegmann, 2009). The characteristic travel distance (CTD) represents the potential of a chemical to be transported over long distances in air or water (distance at which the concentration of chemical decrease to 37% due to transport). The transfer efficiency (TE) is a

[11] http://www.epa.gov/oppefed1/models/water/kabam/kabam_user_guide_appendix_d.html

[12] http://www.vega-qsar.eu/index.php

dimensionless metric of potential for atmospheric transport and deposition of parent compound in terrestrial and aquatic environments of a remote region. The OECD Tool requires estimated degradation half lives in soil, water and air, and log Kaw and log Kow as chemical-specific input parameters. According to US EPA (2009) there are considerable uncertainties in the environmental fate properties (input values) of the selected chemicals under consideration, and the results indicate that dicofol and its breakdown products have Pov lower and LRTP properties similar to those of several known POPs. P,p'-DDT, aldrin and endrin display a Pov of 1010, 225 and 1556 days, a CTD of 2530, 206 and 515 km and a TE of 5.17, 0.003 and 0.04%. The Pov, CTD and TE for o,p'-dicofol and p,p'-dicofol were 37 and 138 days, 2142 and 1467 km and 9.45 and 3.39%, respectively. For the metabolites model predictions for DCBP, FW-152 and DCBH were 172, 516 and 108 days for Pov, 1381, 504 and 238 km for CTD and 2.24, 2.15 and 0.66 % for TE.

64. The most recent LRT potential was assessed by Li et al. (2015) with the Globo-POP model. Li et al. (2015) summarized that dicofol, relative to other Arctic contaminants, exhibits a moderate 'absolute Arctic Contamination Potential' ($eACP^{air}_{10}$) and the highest 'relative Arctic Contamination Potential' ($mACP^{air}_{10}$), indicating that it can be transported from source locations to the Arctic environment with moderate efficiency, that its persistence is more influenced by temperature with cold temperatures in the Arctic favouring slow degradation and relative enrichment, whereas warm temperatures near the equator favour fast degradation. Based on the simulated total dicofol mass that resides in the Arctic surface media (M_{Arctic}) after a decade of continuous emission, $eACP^{air}_{10}$ is defined as the percentage of M_{Arctic} in the cumulative global emission. $mACP^{air}_{10}$ is defined as the percentage of M_{Arctic} in the total dicofol mass remaining in the entire global environment by end of the tenth year. Dicofol has a similar eACPair10 (0.06%) compared with HBCD (0.05%) or aldrin (0.04%). The $mACP^{air}_{10}$ for dicofol (3.7%) was higher than lindane (3.39%) and DDT (2-3%). The rate of decline of dicofol concentration in the Arctic lags behind the rate of decline in global dicofol usage, indicating modelled accumulation in the Arctic as a result of slowed temperature-dependent degradation according to the model results (Li et al. 2015).

Confirmation based on measurements in remote areas

65. Zhong et al. (2012) provides evidence of dicofol in environmental media remote from sources, based on a study carried out on surface seawater and marine boundary layer air data collected during a cruise from the East China Sea (33.2°N) to the high Arctic (84.5°N). Dicofol was detected in air (predominantly gas phase) and in seawater (cf. section 2.3).

Summary of for long-range environmental transport

66. Dicofol has a calculated half-live between 3.1 and 4.7 days that is a screening indicator for LRT. Model results showed that dicofol can be transported to remote regions and displayed LRT properties similar to those of several known POPs. Limited evidence of dicofol in environmental media from remote sources (one study) is available.

2.3 Exposure

2.3.1 Environmental monitoring data

Remote areas

67. In a large scale study from East Asia to the high Arctic Ocean, dicofol was abundant found along with the already listed POP α-endosulfan and detected in average levels of 14 ± 29(SD) pg/m^3 in air and 9 ± 23(SD) pg/L seawater (Zhong et al. 2012). Concentrations decreased from ~25 pg/m^3 and 87 pg/L at 35°N to 0.9-2.5 pg/m^3 and <0.2-2 pg/L at 66-80°N latitude in air and seawater, respectively. The authors used the data to calculate air-water fugacity ratios at each of the sampling locations which provide information on the likely net direction of chemical transfer. It was suggested that air was the dominant mode of transport, with dicofol being carried from original source and deposited into surface water at all points along the cruise, although deposition rates were highest close to potential source regions. Zhong et al. (2012) performed a polar extract of the samples and a GC injection technique (pulsed splitless) that helps to prevent thermal breakdown of dicofol. Moreover they used an internal dicofol standard and an isotope labelled surrogate (but not dicofol-D8). Therefore, and supported by discussions with experts and clarification by the authors (G. Zhong, personal communication, April, 2015), the study results seem to be plausible, based on the applied analytical method.

68. Levels of dicofol and DCBP (could not be separated analytically) in Canadian archipelago Arctic air were ~2 pg/m^3 during ArcticNet cruises in 2011-2013 (L. Jantunen, Environment Canada, personal communication, 2015). Hoferkamp et al. (2010) were unable to find any results for dicofol in Arctic environmental media. Muir and de Wit (2010) stated that there were no direct measurements of dicofol in the Arctic. Among other reasons the analytical problems of dicofol could be involved in this

observation. Kucklick (J. Kucklick, personal communication, November, 2013) mentioned for example the difficulties of detecting dicofol in seal samples.

Regional and local scale

69. In air and seawater of the Bohai and Yellow Seas, China, dicofol was frequently detected. Gas phase atmospheric concentrations averaged 3.8±2.3 pg/m^3, whilst particulate concentrations were lower averaging 0.68 pg/m^3 (Zhong et al. 2014). Dissolved seawater concentrations averaged 63±65 pg/L with highest concentrations up to approximately 240 pg/L. Zhong et al. (2015) analysed dicofol in 72 surface sediment samples from the coastal and offshore regions of the Bohai and Yellow seas, which border on regions of high pesticides consumption and production and are exposed to huge amounts of runoff and sediment load of several rivers. Dicofol was detected in 60% of the samples and dominated the concentration profile with 90% of the reported concentrations greater than 100 pg/g dw, an average concentration of 1,300±2,500 pg/g dw and a highest concentration of 18,000 pg/g dw. Concentrations generally reflected those measured in air and water with higher values closer to estuaries indicating on-going riverine sources including inputs from local areas of production.

70. In sediments in California's Central Valley, dicofol was found in 75% of the 28 tested samples up to 250 ng/g (Weston et al. 2013). In an earlier publication (Wang et al. 2010) dicofol was detected in five out of 12 sediment samples from California's Central Valley with reported concentrations of 36±207 (mean±SD) ng/g dw. In lower regions of Yangtze River, Tang et al. (2013) detected dicofol levels of 0.46±1.38 (mean±SD) ng/g dw in the sediment, whereas the dicofol levels in the surface water where below the detection limit (<0.28 ng/L).

71. In a national survey in France, dicofol was not detected in any of 154 sediment sampling points (Vulliet et al., 2014). This observation is in line with the findings of Thomas et al. (2012), where dicofol was not detected in freshwater fish and sediments from fish ponds in north-eastern France.

72. In a vineyard watershed in France, Sabatier et al. (2014) reconstructed the long term levels of dicofol in lake sediment. Concentrations showed peaks in 1970, 1992 and 2000 reaching fluxes of approximately 4.5, 8.0, 6.0 ng/cm^2/y, respectively. In transboundary aquifers in North-eastern Greece, dicofol was detected in one out of 37 wells above the EC drinking water quality standards limit of 0.1 µg/L, at a level of 0.153 µg/L (Vryzas et al. 2012). Papadakis et al. (2015) examined 416 water samples from six rivers and ten lakes in the main cultivation areas of Greece (collected from Sep. 1999 to Feb. 2001) and calculated annual average concentrations for dicofol in surface water bodies of 0.01µg/L, which exceeds the annual average for EU Environmental Quality Standard for dicofol (0.0013 µg/L) according to Directive 2013/39/EC.[13]

73. Bishnu et al. (2009) detected dicofol in the water bodies in tea gardens in the Doars region of West Bengal, India, in April, at a mean level of 3.6 (range 0.9–5.8) µg/L. Domagalski (1996, cited in US EPA 2009) reported for an analysis of water samples from San Joaquin River (California) and its tributaries that all samples collected between March and June 1993 were below detection limits but in June to September 33 samples were found above the detection limit (0.05 µg/L) with max concentrations of 2.5 µg/L. From 1990-2006, 618 samples from surface waters were analysed for dicofol in the California Department of Pesticide Regulation (CDPR) database. Of these, dicofol was detected in 11 (1.8%) of the samples, with a maximum concentration of 0.27 µg/L (US EPA 2009). The Pesticides in Ground Water Data Base (US EPA 1992, cited in US EPA 2009) showed no detections of dicofol in limited sampling in several States, including California (1634 wells sampled between 1979 and 1991).

74. Syed and Malik (2011) detected dicofol in surrounding surface soils of an industrial site in Pakistan in 69% of 36 samples at a mean level of 10.75 ng/g, although it is not quite clear to what extent these levels originate from industrial production processes (including waste dumping) or from agricultural use in this area. .

75. Weaver et al. (2012) found dicofol in surface soil (one sample was analysed for dicofol measuring 18 µg/kg) from the Namoi Valley, Australia. Dicofol was measured at up to 53.2 pg/m^3 in urban air in Spain (Coscolla et al. 2011).

76. Dicofol levels (highest mean concentrations) in biota in crop areas with historical dicofol use have been reported by the US EPA (2009) for small mammals (up to 1.4 µg/g, Florida), terrestrial invertebrates (up to 3.9 µg/g, California) and reptiles/amphibians (up to 3.8 µg/g, Florida). In non-crop areas the highest mean concentrations of dicofol were 0.3 µg/g for small mammals, 0.76 µg/g for terrestrial invertebrates, 0.38 µg/g for reptiles/amphibians, 0.9 µg/g in birds and 0.26 µg/g for fish. In

[13] http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32013L0039

New York dicofol was detected in earthworms at a level of 1-2 µg/g. In eggs collected from thirteen avian species in California, Florida and New York, the yearly mean levels for dicofol, p,p'-FW 152 and p,p'-DCBP ranged from 0.003 - 0.46, 0.002 - 0.218, and 0.004 – 0.165 µg/g, respectively (US EPA 2009). The dicofol levels found by Malik et al. (2011) in eggs of cattle egret, prey samples and sediment in Pakistan are described in section 2.2.2. Dicofol was also frequently detected in liver samples from six species of predatory birds of the Canary Island, Spain with concentrations ranging from 0.001 to 0.0095 µg/g ww (Luzardo et al. 2014).

77. In animal feed samples in India, dicofol was found at mean concentration ranging from 0.03 to 0.34 µg/g (Nag & Raikwar 2011). Dicofol has been shown to accumulate in cows' fat and milk (Shaffer 1987, unpublished): 0.5 µg/g of p,p'-dicofol in the fat after 29 days of 10 µg/g in food. In mutton bird in New Zealand, dicofol was not found in any of the analysed samples (Bekhit et al. 2011). However, if DCPB is not reported, dicofol measurements may likely underestimated due to the breakdown of dicofol to DCPB during sample analysis.

DDT and related compounds from dicofol production and use

78. Dicofol can contain DDT and related compounds depending on the manufacturing method (UNEP/POP/POPRC.10/4). The ratio of o,p'-DDT/p,p'-DDT can indicate dicofol as source of DDT (use of dicofol or DDT). For ΣDDT originating from technical DDT a ratio of 0.2 to 0.3 is typical, whereas a ratio of 1.3 or higher (mean ratio 7) indicates technical dicofol as source (Qiu et al. 2005; Qiu and Zhu 2010). The following discussion below focuses on data pertaining to the use of technical dicofol.

79. The ratio of o,p'-/ p,p'-DDT has been used in literature to distinguish between DDT and dicofol as source of ΣDDT. But to use isomer ratios for the estimation of their emission source, the environmental fate of the two isomers should also be taken into consideration (e.g. differing volatility from soil to air, stability in soil, air water fluxes and bioaccumulation). However, Ricking and Schwarzbauer (2012) claim that the potential to follow the environmental fate of ΣDDT via isomer composition has not been realized accurately so far and, consequently, has not been well established in the field of environmental chemistry. In case of the ratio of o,p'-/ p,p'-DDT the 4.7-fold higher water solubility and 7.5-fold higher vapour pressure of the o,p'-than the p,p'-isomer (Ricking and Schwarzbauer, 2012) have to be considered. Regarding the half-life of the isomers further studies are needed (Qiu et al. 2005). A faster metabolization of o,p'-DDT in the environment is reported by Martin et al. (1993, in Li et al. 2006), whereas in Bidleman et al. (2013) a preferential degradation of p,p'-DDT versus o,p'-DDT is mentioned. Hence, source correlations far away from areas of dicofol use have to be interpreted cautiously. On the other hand the fact that dicofol is one source of current DDT pollution cannot be neglected.

80. Dicofol as source for ΣDDT was suggested by the authors for sediments from Yangtze River Estuary and the adjacent East China (Zhou et al. 2014a), for surface sediments in Pakistan (Syed et al. 2014), in an Eurasian Eagle owl population from south-eastern Spain (Gomez-Ramirez et al. 2012) and mussels collected from a Spanish estuary (Suarez et al. 2013).

81. In more remote areas ΣDDT possibly originating from dicofol exposure was found in air in a mountain of the Tibetan Plateau of China (Zhu et al. 2014); in soil, lichen, conifer needles and bark of the Southeast Tibetan Plateau (Yang et al. 2013) and potentially in the Kara Sea (Russian Arctic) possibly originating from the Ob and Yenisei Rivers (Carroll et al. 2008). The analysis of an extensive database of organochlorine (OC) pesticide concentrations measured at the Norwegian Arctic monitoring station at Svalbard revealed an increasing trend in o,p'-DDT/p,p'-DDT ratios in the Arctic atmosphere, which may indicate a shift from use of technical DDT to dicofol (Becker et al. 2012).

82. In contrast to the findings above, there are also studies existing, which state that the DDT residue ratios are indicating technical DDT as the source rather than dicofol (Qu et al. 2015, Yu et al. 2014, Ding et al. 2009). Monitoring results from the Portuguese coast showed no predominance of o,p'-DDT and therefore Mizukawa et al. (2013) estimated no dicofol induced DDT pollution for this region. The ratios of o,p'-DDT/p,p'-DDT in marine fish from the South China Sea were <1, suggesting that dicofol was unlikely the source of DDT (Hao et al. 2014).

2.3.2 Human Exposure

83. Dicofol has been measured in breast milk in China (geometric mean = 9.63 ng/g lipid; max = 64 ng/g), Korea (mean =1.87 ng/g, max =2.96 ng/g) and Japan (mean = 0.32 ng/g; max = 2.65 ng/g) (Fujii et al. 2011); and in adipose tissue in 75-95% of people tested in 3 regions of China, with a maximum value of 559 ng/g and means of 9.06, 2.91, and 4.82 ng/g (Wang et al. 2011). Elevated ratios of o,p'-DDT to p,p'-DDT in breast milk in China is suggested to result from dicofol exposure (Haraguchi et al. 2009, Wang et al. 2014). In Spain dicofol was detected in 27.8% of 18 colostrum

samples with concentrations ranging between 0.12 and 0.59 µg/L (median 0.35 µg/L), but was not detected in 13 major human milk samples from the Canary Islands (Luzardo et al. 2013b).

84. Chen et al (2014) analysed 10 human milk samples collected from anonymous donors in 2010-2011, 10 cow milk samples and 10 baby formula samples purchased from local stores in USA. In all analysed samples, p,p-dicofol, o,p-DDE, p,p-DDE, chlorpyrifos and hexachlorbenzene were found. Detected p,p-dicofol concentrations ranged between 0.033 and 0.230 ng/ml (median 0.091 ng/ml) in cow milk, 0.029 and 1.115 ng/ml (median 0.109 ng/ml) in human milk, and 0.029 and 0.096 ng/ml (median 0.047 ng/ml) in baby formula.

85. The concentration of organochlorine residues was measured in pasteurized milk from Mato Grosso do Sul, Brazil. Of the 100 composite samples analysed, dicofol was detected in 14% in the range of 2.75–9.61ng/g lipid with a mean concentrations of 5.11ng/g lipid (Avancini et al. 2013).

86. Luzardo et al. (2013a) investigated the presence of organochlorines in locally produced eggs from different production sites (conventional, free-run and organic; n=12 each) collected in 2012 from supermarkets and stores for organic food in the Canary Islands (Spain). All analysed samples contained low but quantifiable levels of organochlorine pesticides. Dicofol was present in 75% of eggs from conventional production (range: n.d.-8.42 ng/g; median: 0.93 ng/g), in 41.7% of eggs from free-run production (n.d.-1.08; 0.57), and in 58.3% of eggs from organic production (n.d.-2.31; 1.07).

87. Wang et al. (2013) examined pesticide residues including 33 different pesticides in market vegetables (n=285) in Shaanxi Province of China by GC. Dicofol was detected in 1.05% of the samples in both green pepper and chives samples. In Bangladesh 210 samples of 8 types of vegetables collected in 2009-2012 were analysed for 19 agricultural pesticides. Dicofol was detected only in one sample (cucumber) at a concentration of 0.14 mg/kg (Chowdhury et al. 2013). Yan et al. (2014) detected dicofol in four of nine celery samples in local markets of Baoding, Korea at levels of 3.6, 2.5, 2.5, and 3.4 ng/g.

88. According to European Food Safety Authority (EFSA) 2011 appropriate analytical methods for the detection of dicofol were lacking, which may result in underreporting of residues. They suggested measurements e.g. in plant commodities: o,p'-dicofol, p,p'-dicofol and their corresponding DCBP, for milk from ruminants sum of dicofol (sum of o,p'- and p,p'-isomers) and FW-152. A new analytical method was published from the European laboratories for residues of pesticides in 2013 (EURL-SRM, 2013). Therefore, data reported before 2011 might be less sensitive and negative results in these studies might not be an indication of lack of exposure. In processed commodities the major degradation product seemed to be the corresponding DCBP, but formation of chloroform under boiling and sterilization conditions cannot be excluded (EFSA 2011).

89. The 2013 European Union report on pesticide residues in food of EFSA documented dicofol detections in 0.15% of the samples. Highest mean concentrations have been found in mandarins with 0.02 mg/kg. Highest concentrations were detected in strawberries with 0.04 mg/kg (EFSA 2015).

90. Lozowicka (2015) investigated 696 samples of Polish apples in the period of 2005–2013 (182 samples for pesticides). Dicofol was detected in 4 samples and the median of the four residue levels (above the LOQ) was 300% higher than the maximum allowable residue level. The highest measured value was 0.156 mg/kg (EFSA 2013).

Consumer Exposure and Risk Assessment

91. In 2011 EFSA reviewed maximum residue levels for dicofol (EFSA 2011). As dicofol is no longer registered in the EU, only the Codex limits (CXLs) were considered in the calculations of the consumer exposure. Assuming the toxicological reference values, the highest chronic exposure was calculated for the Dutch children, representing 1379% of the acceptable daily intake (ADI of 0.002 mg/kg bw). Exceedances of the acute reference dose (ARfD of 0.15 mg/kg bw) were also identified for the existing CXLs in oranges, grapefruits, mandarins, table grapes, lemons and peaches. Excluding CXLs for these commodities and those not sufficiently supported by data from the calculation, the highest chronic exposure still represented 258.1% of the ADI for the French population. When only considering the CXL for tea (50 mg/kg), the highest chronic exposure declined to 95.7% of the ADI for Irish adults; the highest acute exposure is then calculated for tea, representing 30.7% of the ARfD. It has been stated that CXLs considered for consumer risk assessment were actually based on European uses of dicofol that are no longer authorised, except for tea, for which the notifier made a specific request (EFSA 2011).

Summary of human exposure

92. Due to the chemical instability of dicofol in solution as well as limitations in analytical methods reported dicofol measurement values may result in underreporting. However, dicofol and/or

its metabolites have been detected in milk, baby formula, eggs, fruits, vegetables, human breast milk, colostrum and blood. Exposure calculations based on Codex limits revealed up to 13.9 fold exceedances of the TDI for the population group with the highest exposure.

2.4 Hazard assessment for endpoints of concern

Adverse effects on aquatic organisms

93. Dicofol is highly toxic to aquatic animals as defined in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNEP/POPS/POPRC.10/10). It is classified as aquatic acute and chronic category 1 in the European Union's regulation on the classification, labelling and packing of substances and mixtures (Regulation (EC) No. 1272/2008). According to OSPAR (2002) the lowest LC50 for fish is 0.053 mg/L; the lowest value for crustaceans is 0.08 mg/L, and the no observed effect concentration (NOEC) in a 300-d chronic exposure of fish was 0.0045 mg/L. US EPA (1998) cites effects on the reproductive physiology of the fathead minnow from concentrations as low as 0.0055 mg/L.

94. Dicofol acute toxicity ranges from very highly toxic to highly toxic to freshwater fish and invertebrates under acute exposure conditions (Annex E information, USA, 2015). The LC_{50} values for seven species of fish range from approximately 0.05 to 0.6 mg/L, whereas for invertebrates (*Daphnia magna*) an EC_{50} of 0.14 mg/L was observed (US EPA, 2009). Chronic exposure to freshwater animals resulted in adverse effects on growth and reproduction in multiple fish species with a no observed adverse effect concentration (NOAEC) of approximately 0.004 mg/L (95d-NOEC= 0.0044 mg/L) and on survival in amphipod with a NOAEC of 0.019 mg/L (US EPA 2009). For rotifers the 11d-NOEC for growth rate was 0.2 mg/L, and for the maximum population density in correlation with the food density 0.1 mg/L and 0.2 mg/L for the lower and the higher food amount, respectively (Xu et al. 2014).

95. In a comparative analysis between fish and mice (Grisolia 2002) erythrocyte micronuclei assays, injection of the dicofol formulation Kelthane 480 CE induced a significant increased micronucleus frequency in the fish *Tilapia rendalli* (from 25 mg/kg), but not in mice (up to 200 mg/kg).

96. Regarding the acute toxicity values of dicofol metabolites, the 96h-LC_{50} values for rainbow trout are >2.29 and 0.24 mg/L for p,p'-DCBP, and p,p'-FW-152, respectively (Spain, 2006). The 96h-LC_{50} of p,p'-FW-152 is in the range of those reported for dicofol.

Adverse effects on terrestrial organisms

97. In terrestrial species, dicofol induced chronic effects including parental systemic and reproductive effects in rat (NOAEL 0.4 mg/kg bw/day). Dicofol is non-lethal to the adult honey bee on an acute exposure basis (LD50 > 0.05 mg/bee) (US EPA 2009). However, task-dependent behavioural effects on learning have been observed in honeybees when exposed to sublethal concentrations of dicofol (Stone et al. 1997). For earthworms (*Eisenia foetida)* a LC50 of >354 mg/kg dw was reported (UNEP/POPS/POPRC.8/INF/13). A two-generation study of reproductive and morphoiogical effects of o,p'-dicofol on captive American kestrels by MacLellan et al. (1996) showed for females exposed to 5 and 20 mg/kg bw significantly thinner egg shells at 20 mg/kg of o,p'-dicofol. Male embryos from females dosed with 5 and 20 mg/kg bw of o,p'-dicofol had gonads that were significantly ($p<0.05$) different from those of control chicks, indicating feminization by the presence of primordial germ cells. Wiemeyer et al. (2001) reported that the lowest observed dietary effect concentration for eggshell thinning was 3 mg/kg ww diet and that the NOAEC was 1 mg/kg ww diet for a dicofol formulation without any measureable ΣDDT. US EPA (2009) also reported the LOAEC of 3 mg/kg diet and NOAEC of 1 mg/kg diet) based on decreased egg shell thickness. According to the OSPAR document on dicofol (OSPAR 2002), the pattern and magnitude of dicofol (0.0334 mg/g, <0.1% ΣDDT) on eggshell thinning was similar to that observed with p,p'-DDE. Schwarzbach et al. (1988, cited in OSPAR, 2002), showed that dicofol was not metabolized to DDE in birds and therefore concluded that the adverse effect (egg shells became progressively thinner with increasing time of exposure) was caused by dicofol itself.

98. In embryonic livers of *Gallus domesticus*, a formulation of dicofol (Colonel-S® 18.5%) applied as solution in which the eggs were immersed for 60 min on day 0 and 4 of incubation at concentrations of 250, 500 and 1000 mg/L induced severe biochemical and histological alterations (e.g. extensive cell degeneration and necrosis with enlarged blood sinusoids, cytoplasmic vacuolization, and leucocyte infiltrations with congestion or dilation of central vein, decrease in the levels of total protein, glycogen, and glutathione content and an increase in alkaline phosphatase activity) (Bhaskar et al. 2014). The survival rate of chick embryo was reduced and the number of malformations was exhibited by a formulation of dicofol (18.5% EC) applied at concentrations of 250,

500 and 1000 mg/L (Nitu et al., 2012). In both studies concentrations were selected in correlation to the recommended application rate (500 mg/L) for the products used in plant protection practise and indicate adverse effects of short time exposure of eggs to dicofol, although it is unlikely that this exposure scenario (immersion of 60 min in a dicofol solution) will appear during direct overspray in field. In-ovo exposure to dicofol resulted in damage of Japanese quail reproduction, mainly through eggshell thinning in dosages of 0.0003, 0.001 and 0.003 mg/g of egg (Kamata et al. 2010).

99. According to the US EPA (2009) risk assessment of dicofol use, risks to aquatic invertebrates, fish, aquatic-phase amphibians, terrestrial-phase amphibians and mammals were identified. A risk due to indirect effect based on habitat effects was identified for the federally threatened California red-legged frog (*Rana aurora draytonii*).

Summary of ecotoxicological effects

100. Dicofol is highly toxic to aquatic animals ($NOEC_{fish}$ = 0.0044 mg/L) and can severely affect the reproduction in birds (e.g. eggshell thinning and feminization of male embryos). The acute toxicity values of the dicofol metabolites p,p'-DCBP and p,p'-FW-152 (96h-LC_{50fish} = >2.29 and 0.24 mg/L, respectively) are indicating for p,p'-FW-152 high toxicity to fish. Endocrine related effects have been observed in a broad range of tests with cells originating from different animal species as well as of human origin.

Adverse effects on human health

101. The toxicity of dicofol was assessed by WHO 1996, 2009, EPA 1998, IARC, 1998, the European Union in the frame of the assessment of active substances in plant protection products, 2006, JMPR, 2011. An acceptable daily intake (ADI) of 0.002 mg/kg has been derived (JMPR 2011). A chronic reference dose of 0.0004 mg/kg bw/day has been established by EPA (EPA, 1998). An acute reference dose of 0.15 mg/kg has been established by Spain, based on neurotoxicity in rats (Spain, 2006, EFSA, 2011). EPA established an acute reference dose of 005 mg/kg bw (EPA, 1998). Several toxicity studies on dicofol had been published before 1980, with a dicofol preparation with lower purity degree (below 95 % containing more than 0.1 % DDT relating impurities) and therefore may not be currently marketed any more (WHO, 1996). However, as depicted in section 2.1.1 this might not be true for all countries. The DDT contaminant could have been contributed to the effects seen in the older studies.

102. Classification and labelling: Dicofol is classified for its hazards to human health according to the Globally Harmonized System as acute toxic, category 4, H302 (harmful if swallowed) acute toxic, category 4, H332 (harmful if inhaled) skin irritant, category 2, H315 (causes skin irritation) and sensitising to skin, category 1, H 317 (may cause an allergic skin reaction) (EC 2015).

103. Metabolism and toxicokinetics are well described in WHO (1992), US EPA (1998) and JMPR (2011). Single doses of 25 mg/kg were administered to male mice. Approximately 60% of the administered dose was eliminated within 4 days primarily in the faeces. Faecal excretion accounted for 40% of the administered dose whereas urinary excretion accounted for 20%. Peak tissue concentrations were reached within 24-48 h. The highest concentrations of the radiolabelled compound were found in adipose tissue followed by liver, kidney, lung, heart, blood plasma, brain, whole blood, and spleen Concentrations dropped rapidly over 4 days except in adipose tissue (Kaneshima et al., 1980). Metabolism studies in rats were performed with radiolabelled dicofol, administration of high (50 mg/kg bw single treatment) and low (0.5 mg/kg bw for 16 days) doses were eliminated mainly with the faeces, and stored in adipose tissue. The metabolic pathways for dicofol were deduced, with the major one involving reductive halogenation to dichlorodicofol and oxidation to dichlorobenzophenone, dichlorobenzoic acid, and dichlorobenzil . The analysis of metabolites revealed at most 0.2% of the radioactive residue was DDE which could be contributed by the presence of DDT (0.2%) and DDE (0.01%) in the test material. The data indicated that dicofol metabolized differently from that of DDT, which is metabolized to the purported carcinogen, DDE (US EPA 1998).

104. Dietary feeding for 12 weeks (32 ppm) of rats had demonstrated, that after 8 weeks an equilibrium in fat (at 25 ppm for males and 70 ppm for females) was reached. After 12 weeks dicofol was withdrawn and concentrations declined, whereas in males it was zero after 14 weeks, but remained at about 6 ppm in females. Also higher and lower levels in the diet were stored to a higher extent in females than in males (IPCS, 1992).

105. Main adverse effects observed in short term dietary studies with laboratory rodents were on the liver, adrenals and the thyroid. The NOAEL in rats was 0.07 mg/kg bw/day and in mice 1.6 mg/kg bw/day. In dogs, target organs for dicofol toxicity were the adrenals, liver, heart and testes. The NOAEL was 0.29 mg/kg b.w./day. Cortisol response to ACTH was reduced; the LOAEL for these

effects (decrease in Cortisol release and oligospermatogenesis) was 3.3 mg/kg bw/day.(WHO, 1996). A 1-year dietary study in dogs (was reported with a NOAEL of 0.12/0.13 mg/kg bw/day (males/females) based on inhibition in ACTH stimulated cortisol release at 0.82 mg/kg bw/day. Dermal application in short term tests in rabbits (4 weeks/6 hours/day, 5 days/week) resulted in a NOAEL of 4 mg/kg bw/day (based on decrease in body weight) and in rats (13 weeks 6 hours/day, 5 days/week) of 4 mg/kg, based on liver hypertrophy (US EPA 1998).

106. Jadaramkunti et al. (2002) reported toxicity on testes and accessory reproductive organs in rats at doses of 400 mg/kg of a dicofol formulation administered by gavage for 30 days. Chan et al. (2009) examined the ability of dicofol to induce cytochrome P450 by treating 6-weeks old male Wistar rats with 1, 10 and 25 mg/kg dicofol intraperitoneally for four days performing histopathological evaluations, enzyme assays, gel electrophoresis and immunoblotting, reverse transcription-polymerase chain reaction (RT-PCR) analysis, and a sleeping time study (not conducted with 1 mg/kg bw). Thus, results of the study demonstrated that dicofol induces CYP1A1, CYP2B, CYP2E1 and CYP3A in rat liver and increases phenobarbital metabolism and CCl4 toxicity in rats at 10 and 25 mg/kg bw with a dose dependent increase.

107. The genotoxicity of dicofol was tested in a series of in vitro and in vivo tests. Negative results were obtained from gene mutation assays, however some limitations due to negative results of the positive control and the purity of the test substance were reported. Dicofol was also negative in in vitro and in vivo chromosome aberration and unscheduled DNA synthesis tests (WHO 1996, 2006). According to testing information of the NTP for dicofol, positive results in mouse lymphoma assays were found (IARC 1998; NTP 1978, 2015).

108. Dicofol was cytotoxic to human lymphoid cells at a concentration of 10^{-4} to 10^{-6} M (molar). In cultures incubated with 10^{-5} M dicofol, MI metaphases were as high as 13% compared to less than 1% in controls indicating an effect on cell cycle kinetics. Statistically significant increases in sister chromatid exchange frequency was seen in cells exposed to dicofol at 10^{-5} and 10^{-6} M (Sobti et al. 1983).

109. The European, US and IARC reports are in agreement that the dietary carcinogenicity studies performed with dicofol are negative in rats but positive in male mice at the highest dose (Spain, 2006, US EPA 1998, IARC, 1998). A bioassay for possible carcinogenicity carried out by the National Cancer Institute in the US reported statistically significant increases in hepatocellular carcinomas in dosed male mice, and the Institute concluded that dicofol was carcinogenic in male mice (NTP, 1978). Hepatocellular adenomas and carcinomas were observed at doses of 39.6 and 79.2 mg/kg bw/day treated for 45 weeks in males. No tumours were observed in females treated with 18.3 or 36.5 mg/kg/day (NTP 1978, US EPA 1998). This resulted so far in no EU GHS classification, an US group C, possible human carcinogen classification and an IARC conclusion that the available data are insufficient to evaluate the carcinogenicity of dicofol to humans.. From the long term study in rats a NOAEL of 5 ppm corresponding to 0.22 mg/kg bw/day was established on the basis of changes in liver and adrenal glands.

110. The reproductive toxicity was assessed in rats and rabbits. In a two generation reproduction study in rats a NOAEL of 0.4 mg/kg/day was established based on ovarian vacuolation in the F1 generation at 1.9/2.1 mg/kg/day in M/F; the NOAEL for offspring was 1.9 mg/kg bw/day based on reduced viability at 9.5/10.5 mg/kg bw M/F. The NOAEL for parental toxicity was 0.4 mg/kg/day; the LOAEL based on liver hypertrophy in both generations was 1.9/2.1 mg/kg/day in M/F. In a one generation postnatal toxicity study in rats a NOAEL of 1.7/2.0 mg/kg bw/day M/F for parents and offspring based on liver pathology seen at the LOAEL at 8.7/9.8 mg/kg bw/day M/F was derived. In a study in rabbits a NOAEL of 4 mg/kg bw/day for maternal and developmental toxicity was observed; the LOAEL was 40 mg/kg/day, based on an increased incidence of abortions in the does. A rat developmental toxicity study established a maternal NOAEL of 0.25 mg/kg bw/day, maternal effects were detected at 2.5 mg/kg bw/day whereas no developmental toxicity was observed at the highest dose of 25 mg/kg bw/day (US EPA, 1998). Toxic effects in offspring were not observed at maternal non-toxic doses, which would be indication for reprotoxicity. Exposure to dicofol at 2.5 mg/kg for eight weeks significantly reduced sperm motility in male Lewis rats. Sperm morphology, daily sperm production, sperm transit time through the epididymis, hormonal levels, and histopathological evaluation of testis and epididymis did not differ significantly. A mixture of dicofol and other pesticides at their NOEL also changed sperm motility (Perobelli et al. 2010).

111. Shahani et al. (2013) investigated the teratogenicity of the insecticide Colonel-S, a commercial formulation containing 18.5% dicofol in Swiss Albino mice. The insecticide formulation was orally administrated in a low and a high dose (resulting in a dicofol concentration of 4 and 16 mg/kg bw, respectively) to pregnant female mice during the entire organogenetic period of gestation (day 5-14).

Mice were sacrificed on day 18 of gestation for uteri examination for teratological changes. Treatment showed maternal toxicity (as evidenced by reduced maternal weight gain). A dose related decline in live litter size and rise in percentage of resorbed foetus was shown (low dose: 52.48% high dose 40.74%). In the high dose group, the percentage of alive foetuses was greatly reduced. However, mice from the low dose group did not exhibit significant alterations. The authors conclude that the tested formulation is a developmental toxicant in a dose-dependent manner.

112. Liu et al. (2012b) studied the interaction of dicofol with the globular protein trypsin in aqueous medium. Dicofol was shown to form spontaneously a complex with trypsin mainly by hydrogen bond with one binding site. The change in trypsin conformation was proved. The results indicated that dicofol had potential effects on structure as well as activity of trypsin and that the effects enhanced with increasing dicofol concentration. The results indicate that dicofol has deleterious effects on the frame conformation of proteins and disturbs their physiological function in vitro.

113. Liu et al. (2012a) examined the interaction between dicofol and serum protease α-chymotrypsin (α-CT) in aqueous medium. Three aspects including conformational change, interaction mechanisms and functional change were investigated. Dicofol bonded to α-CT and formed a stable complex unfolding the protein structure and increasing the exposure to chromophore groups in the internal hydrophobic region. Thus, dicofol exposure can lead to conformational changes of α-CT, which can lead to disturbed function and activities of enzymes. The effects enhanced with the increasing concentration of DCF.

114. A screen for nongenotoxic carcinogens identified dicofol as a compound that significantly stimulated phospholipid-dependent protein kinase C (PKC) in the absence of calcium. PKC plays a central role in the signal transduction pathway in cells, and thus is used as a potential marker that could be affected by carcinogens that act via non-genotoxic modes (Rotenberg, 1991). Dicofol was found to be a potent inhibitor of gap junction intercellular communication in in vitro assays (Flodström, 1990). According to the WHO dicofol was found to induce rat liver mixed function oxidase activity and ranked after heptachlor, DDT chlorfenson and dieldrin (WHO 1996).

115. Neurotoxicity was assessed in an acute and a subchronic study in rats. From the acute study a NOAEL of 15 mg/kg bw was established and the LOAEL was 75 mg/kg/.day (based on body weights and reduced food consumptions). At the highest dose observed, 350 mg/kg an increase in the incidence of ataxia and of uncoordinated landing was observed in females. From the subchronic study, the NOAEL was 0.3 mg/kg bw/day and the LOAEL was 5.6 mg/kg bw/day, based on decreased motor activity and increased liver weights. A significant decrease in brain weight was seen in males at 27.8 mg/kg bw/day (US EPA 1998).

Epidemiological studies

116. Settimi et al. (2003) investigated the association between different types of pesticides and prostate cancer in a case control study. They documented an increased risks among farmers exposed to organochlorine insecticides and acaricides (OR=2.5, 95% CI=1.4–4.2), more specifically to the often contemporary used compounds DDT (OR=2.1, 95% CI=1.2–3.8), and dicofol with tetradifon (OR=2.8, 95% CI=1.5–5.0), whose effects could not be well separated. . In general odds ratios (OR) of >1 generally mean that the respective exposure is associated with a higher odds of outcome. Until confirmed by other studies of prostate cancer in relation to past exposure to DDT and dicofol, the present results may be considered statistical artefacts arising from multiple comparisons. Nevertheless, these types of exposures could contribute to the excess of prostate cancer frequently reported among farmers, especially in view of some specific mechanisms of action reported for DDT.

117. Reynolds et al. (2005a) examined in a population-based case-control study early childhood cancer among California children aged 0-4 years who were born between 1990 and 1997 and the residential proximity to agricultural applications of pesticides of the mothers at the time of child birth. Two investigated pesticides were associated with a higher risk for leukaemia when comparing the highest and lowest categories including dicofol (OR: 1-49th percentile 0.75 (0.36–1.55 CI); ≥50th - percentile 1.83; 1.05-3.22 CI). Although they observed elevated risk for leukaemia in highest areas of use of dicofol, some limitations of the study were described; e.g. most children included in the study lived in areas with no or very low agricultural pesticide use; therefore the odds ratios for the highest exposure categories were based on small numbers.

118. Reynolds et al. (2005b) also evaluated in a case control study associations between rates of lympho proliferative malignancies among children from areas of intensive agricultural pesticide use in California, USA. Seven individual pesticides, ranked highest for toxicity and usage (dicofol among others) were separately analyzed. Among the investigated study population, children with Hodgkin's disease (n=258) were slightly elevated in areas with highest use of dicofol 1st-74th percentile OR: 0.77

(0.41–1.45 CI) versus ≥74th percentile OR: 1.43 (0.70–2.95 CI). The authors described limitations as well, e.g. the suitability of proximity as indicator of exposure and the small number of cases may have resulted in the association not being statistically significant.

119. Roberts et al. (2003) evaluated the hypothesis of the association between the maternal residence near agricultural pesticide applications during key periods of gestation and the development of autism spectrum disorders (ASD) in a case control study in children. Comparisons between children of mothers living within 500 meters of field sites with the highest nonzero quartile of organochloride use (endosulfan and dicofol) and children of mothers not living near field sites by multivariate a posteriori models suggested an Odds Ratio for ASD of 6.1 (95%CI 2.4-15.3). The risk for ASD increased with the percentage of organochlorine applied and decreased with increasing distance from field sites. Study authors noted this finding was not statistically significant and was based on a relatively small number of cases. Also it is noted that the RR was not increased for leukaemia. Although taking into account that the proportion of mothers living in proximity to pesticide applications during the defined time periods of interest was small in the study the possible connection between gestational exposure to dicofol and ASD gives reason for concern.

Neurotoxicity in humans

120. Several case reports on accidental exposure to dicofol describe effects of nausea, dizziness, weakness and vomiting. One case of poisoning of a 12 year old boy who was accidentally exposed to dicofol when he fell into a puddle of spilled undiluted dicofol formulation has been published. Initial symptoms were nausea, dizziness, disorientation, confusion, lethargy, and headache. The patient demonstrated horizontal nystagmus and impaired balance. These symptoms resolved within three weeks. Eight months after exposure impairment of certain cognitive functions including auditory attention, immediate memory, and ability to selectively inhibit inappropriate responses were shown (Lessenger and Riley 1991).

121. Mechanistic studies demonstrate that dicofol binds to gamma amino-butyric acid (GABA) receptor–mediated chloride ion channels in nerve cells (Sunol et al. 1998). GABA-mediated neurotransmission is expected to play important roles in gestational brain development.

Immunotoxicity

122. Ohnishi et al. (2008) investigated Kepone, a commercial formulation of dicofol in a study with a mouse macrophage cell line to evaluate the influence on innate immune function of macrophages. It could be demonstrated that lipopolysaccharide-induced activation of the interferon IFN-ß promoter was inhibited. This indicates that dicofol may influence the development of infectious diseases.

Endocrine Disruption

123. Dicofol has been identified as substance with at least some *in vitro* evidence of biological activity related to endocrine disruption (EC 2015). Effects on ovarian vacuolation have been detected at 2.1 mg/kg/day in a two generation study in rats (US EPA 1998). Endocrine disrupting effects have also been detected in a series of in vitro assays using different cell lines from various species. According to the WHO, endocrine disrupting effects are endocrine system related and not necessarily species dependent. Effects shown in wildlife or experimental animals may also occur in humans if they are exposed to EDCs at a vulnerable time and at concentrations leading to alterations of endocrine regulation. Of special concern are effects on early development of both humans and wildlife, as these effects are often irreversible and may not become evident until later in life (WHO 2012).

124. In their discussion of the need for a postnatal developmental neurotoxicity study with dicofol, EPA notes in their 1998 RED that "endocrine toxicity (adrenal and thyroid) was seen throughout the database". Dicofol was issued Tier 1 Endocrine Disruptor Screening Program (EDSP) test orders in 2009; however, the registrant ultimately opted to cancel the technical registration. The issuance of EDSP test orders was based on exposure potential and did not imply any conclusions regarding potential endocrine interaction (Annex E submissions, 2015, USA).

125. The OSPAR Commission listed dicofol as a potential endocrine disruptor in 1998. In 2002 it stated: "There is a lot of evidence of the toxic properties of dicofol and of its effects as an endocrine disrupter." The OSPAR Commission advised that the presence of dicofol in fresh water, even in very small quantities, for most of the growing season may have implications that there will be endocrine disruption of aquatic organisms.

126. One indication for endocrine disruption was a spill of KelthaneR (dicofol), which contained DDT at concentrations as high as 15%, and DDT's metabolites, DDD, DDE, and chloro-DDT into Lake Apopka, Florida. Studies at Lake Apopka spanned two decades, and identified a number of endocrine-disrupting effects on reproductive development in Lake Apopka alligators, in comparison to

the less contaminated reference site. Observations on alligators included a high mortality rate in embryos and neonates, and a higher ratio of oestradiol to testosterone in neonates which lead to histological differences in gonads. The effects seen could not be attributed to dicofol only but were rather mixture related (Guillette et al. 1994; US EPA 1998). A subsequent study on dicofol and other chemicals found in Lake Apopka determined that a mixture of DDT, DDT breakdown products, and dicofol reduced binding to alligator estrogen receptor by 40%. Dicofol alone reduced binding to alligator progesterone receptor by 40%, identifying potential routes by which dicofol, alone or in combination with other chemicals present in the lake, might elicit the endocrine-disrupting effects observed in Lake Apopka (Vonier et al. 1996).

127. Endocrine toxicity was seen also in rats and dogs; affecting the adrenals, the thyroid and ovaries (US EPA 1998; Jadarmkunti & Kaliwal, 1999). An increase of uterine weight in mice was reported by Zhao et al. (2000) as well as proliferation in the human breast cancer cell line MCF7 (Du & Xu, 2001).

128. In carp liver microsomes testosterone glucuronidation was significantly inhibited by dicofol (Lavado et al., 2004). Further it was shown that the synthesis of sex hormones in fish microsomes was influenced by dicofol (Thibaut & Porte 2004).

129. A series of in vitro studies with yeast or cell lines of different origin (e.g. human, hamster, alligator, frog, fish, chicken) have demonstrated that dicofol is able to bind to oestrogen receptors from various species and enhances transcriptional activity. The dicofol metabolite, DCBP showed potent antiandrogenic properties (Thiel et al. 2011). In a competitive binding assay p,p'-dicofol displaced up to 83% of 17 ß-estradiol from alligator estrogen receptor alpha (ERα) and was an equivocal binder to human ERα, displacing a maximum of 58% 17 ß-estradiol (Rider et al. 2010). Several studies have demonstrated that dicofol also interacts with the thyroid hormone receptor and related effects. Dicofol was a powerful inhibitor of the 3,5,3'--triiodothyronine (T3)-uptake system on the plasma membrane inhibiting more than 80% of the saturable initial uptake and significantly depressing the T3 response (Shimada & Yamauchi 2004). Dicofol exhibited a biphasic, nonmonotonic effect on thyroid hormone binding to transthyretins and inhibited T3 binding (Ishihara et al. 2003). It had strong T3- antagonist activity (Sugiyama et al. 2005) and exhibited relatively strong interference with the T4 binding site of transthyretin (van den Berg et al. 1991). An overview on endocrine related effects is provided in an information document to the risk profile.

Summary of adverse effects on human health

130. Dicofol is classified for its hazards to human health according to the Globally Harmonized System as acute toxic, category 4, H302 (harmful if swallowed) acute toxic, category 4, H332 (harmful if inhaled), skin irritant, category 2, H315 (causes skin irritation) and sensitising to skin, category 1, H 317 (may cause an allergic skin reaction). Target organs in short term toxicity tests were the liver, adrenals, the thyroid, heart and testes and the nervous system. Tumours have been observed in male mice at higher dose levels (39.6 and 79.2 mg/kg bw/day) but this finding did not lead to a GHS classification for carcinogenicity. Dicofol is classified as an US group C, possible human carcinogen and an IARC conclusion that the available data are insufficient to evaluate the carcinogenicity of dicofol to humans. Reprotoxic and developmental effects were observed at maternal toxic doses. A NOAEL of 0.3 mg/kg bw has been established based on neurotoxic effects observed in subchronic studies leading to an ADI of 0.002 mg/kg derived by JMPR. The NOAEL of 0.12 mg/kg in dogs based on inhibition of adrenal cortical trophic hormone stimulated release of cortisol in both sexes of dogs was used to establish a chronic reference dose of 0.0004 mg/kg bw/day from US-EPA. In vitro assays demonstrate interference with e.g. confirmation and function of proteins, inhibition of gap junction intercellular communication and immune reactions. Several epidemiological studies have noted associations between dicofol exposure and prostate cancer in men and leukemia, Hodgkins disease and autism disorders in children. Although limitations of these studies hinder causal associations they illustrate the concern that adverse effects associated with dicofol exposure might also occur in humans. Further mixture toxicity of dicofol and other organochlorine compounds may be of concern.

3. Synthesis of information

131. The estimated global dicofol usage decreased from 3,350 t in 2000 to 730 t in 2012. In total 28,200 t dicofol were estimated to be consumed worldwide during this period. Asia was the biggest consumer, accounting for 76.8% (21,700 t). China, by far the largest consumer during this period (19,500 t), showed a reduction of about 75% in its annual domestic usage from 2000 to 2012. In India, the annual dicofol consumption decreased from 145 t to 45 t during this period. An Indian state-owned enterprise still manufactures dicofol with an average annual production output of approximately 50 t.

There is evidence that, although dicofol is being produced in closed systems, improper production practices can result in direct release of DDT to the environment, as can DDT contamination in dicofol, especially if it is above the 0.1% threshold limit. Ongoing dicofol production and usage, and incineration of production waste, can be sources of PCDD/Fs contamination (see section 2.1.3)

132. O,p'-dicofol and p,p'-dicofol hydrolyze relatively quickly at neutral and alkaline pH's as shown by experimental data. However, both isomers are stable under acidic conditions. Hydrolytic stability at pH 5 under laboratory condition does not necessarily imply persistence because susceptibility to biodegradation by microorganisms in environmental media may occur. However, fast hydrolysis rates cannot alone lead to conclude that a substance is not persistent according to ECHA (2014).

133. Photodegradation is not expected to be a significant route of dissipation of dicofol in the environment. Dicofol is not readily biodegradable. Dicofol degrades rapidly in water/sediment systems with a pH >7. No data for water/sediment systems at pH<7 were reported. Experimental evidence suggests that abiotic as well as biotic degradation are dependant on the pH value of the receiving environmental compartment with longer degradation half-lives under acidic conditions. Several laboratory studies reported low mineralisation of dicofol. In laboratory soil simulation tests high DT50 values >180 days (n=3) have been reported for some soils, however also degradation half-lives of 8.5 and 32 days for o,p'- and p,p'-dicofol indicate that dicofol is not expected to persist in soils. Field trials conducted in Florida and California indicated a range of dissipation half-lives of a few days up to 72 days with one reported value of 113 days, depending upon the specific environmental conditions. Based on the physical chemical data the volatilisation and leaching potential of dicofol is considered to be low. No field studies from other locations or colder climates are available.

134. A conservative estimate for persistence of p,p'-dicofol and major degradates of as high as 313 days versus 32 days for the parent compound alone in soil (pH 7.8) was reported by a regulatory body. The UN ECE Task Force on POPs concluded that dicofol is persistent in water at a pH of 5 or below and meets the persistency indicative numerical value of EB decision 1998/2 (UN ECE, 2009). Aquatic ecosystems with acidic water are black water rivers, 14% (pH ≤6), and 3% (pH ≤5) of lakes and rivers in Northern Europe. It can be anticipated that dicofol and/or its degradation products will persist longer in these ecosystems. Recent monitoring data have shown that dicofol is sufficiently persistent to be transported via riverine input to the open sea and one study has measured dicofol in remote regions. Modelled data indicate that the persistence of dicofol in the environment is lower or comparable to benchmark substances and known POPs.

135. The reported log Kow values for dicofol range between 3.5 and 6.6. Based on a screening approach for bioaccumulation potential, a log Kow range of 3.5 to 6.06 and a log Koa range of 8.9 to 10.02, indicates a high bioaccumulation potential of dicofol in both air-breathing organisms and aquatic organisms.

136. In three laboratory BCF studies with bluegill sunfish and common carp, BCF values are 6,100, 8,200 and 10,000 (steady-state calculated BCF of 25,000). Metabolism of dicofol was minimal in bluegill sunfish with an estimated elimination half-life of 33 days. In a full life cycle test the highest observed BCF value was 43,000. Experimental evidence of high bioaccumulation (BCF of 10,000) in invertebrates during 28 days of exposure was shown. Based on experimental studies in fish species dicofol has a high bioaccumulation potential (BCF >5,000). Model predictions for dicofol also suggest biomagnification in terrestrial species; although metabolic transformation was not taken into consideration. Recent monitoring data in heron eggs showed elevated levels compared to prey items, however values were not lipid corrected and therefore no conclusion on biomagnification can be made.

137. If released to air, a vapour pressure and the partitioning coefficients indicate that dicofol will exist in both the vapour and particulate phases in the atmosphere. Atmospheric oxidation by hydroxyl radicals is a possible removal pathway for dicofol in the atmosphere with half-lives of 3.1 to 4.7 days. Model results concerning LRT for dicofol depend on the model used. Whereas the MSC East indicated a lower travel distance and environmental persistence than the benchmark chemical Benzo[a]pyrene, the OECD Pov and LRT tool indicated a characteristic travel distance and transfer efficiency comparable to already identified POPs. The most recent modelling assessment showed that the Arctic contamination potential of dicofol is comparable to known POPs; dicofol can be transported to remote regions with moderate efficacy but results in high calculated enrichment in the Arctic environment. Though monitoring information from remote regions for dicofol is limited, transport via air (mainly in the gas phase but also on airborne particle) and seawater to the high Arctic has been demonstrated in one study. No measurements from biota in remote regions were available. It should be noted that for chlordecone, a substance listed in the Stockholm Convention, the assessment for LRT was based on physical-chemical properties and modelling data (UNEP/POPS/POPRC.2-17 Add.2).

138. Degradation products are considered in the hazard profile of dicofol. This is common practice in the UNEP POP assessment. Major degradates of dicofol with a higher persistence than dicofol include DCBP, FW-152, DCBH, OH-DCBP and DCBA. DCBP, FW-152 and DCBH accumulated in a water/sediment study and can be considered as persistent in sediment. Modelled log K_{OW} values for the metabolites are below the screening value of 5 but according to high log Koa values high bioaccumulation in terrestrial organisms may occur (no metabolism is considered). The estimated bioaccumulation potential for the metabolite FW-152 indicated a BCF >5,000 for fish. The acute LC50 toxicity values of p,p'-DCBP and p,p'-FW-152 for rainbow trout are >2.29 and 0.24 mg/L, the later indicating high toxicity to fish. The metabolite p,p'-DCBP has been shown to reveal potent antiandrogen activity *in vitro*.

139. Dicofol is classified according to the Globally Harmonized System as hazardous for the aquatic environment: aquatic acute H400 (very toxic to aquatic life) and aquatic chronic H410 (very toxic to aquatic life with long lasting effects). The acute toxicity values of dicofol, p,p'-DCBP, and p,p'-FW-152 for rainbow trout (96h-LC50) are 0.053, >2.29 and 0.24 mg/L. The lowest chronic effect concentration of dicofol (95d-NOEC) for fish is 0.0044 mg/L. Among terrestrial species dicofol has a NOAEC for chronic effects in birds and a NOAEL in mammals of 1 mg/kg and 0.4 mg/kg bw/day, respectively.

140. Dicofol has been detected in environmental compartments like seawater, surface waters, air, sediment and soil and in a variety of biota, including fish, molluscs, cattle and birds. But as there are analytical difficulties in the detection of dicofol (e.g. thermal breakdown during analysis, degradation to DCBP and the inability of differentiation from other DCBP sources if only DCBP is detected and degradation at high pH) and these problems may have not been sufficiently addressed, results have to be regarded with caution. In several studies dicofol is indirectly detected via the ratio of o,p'-/p,p'-DDT, but especially in areas with no dicofol use and remote areas, the use of isomer ratios for the estimation of their emission source has to be utilized cautiously.

141. Dicofol levels in biota in crop areas have been reported for small mammals (up to 1.4 mg/kg), terrestrial invertebrates (up to 3.9 mg/kg) and reptiles/amphibians (up to 3.8 mg/kg). In non-crop areas detected values were in earthworms (up to 2 mg/kg), fish (0.26 mg/kg), birds (0.9 mg/kg) and in eggs (annual mean: 0.03-0.46 mg/kg). The detected dicofol levels in fish are well above the laboratory derived acute and chronic effect levels. On a local scale, the environmental concentrations in water bodies in areas of dicofol use (0.0036 mg/L) are in the range of the chronic effect level in fish (NOEC, 0.0044 mg/L). The detected concentrations in birds and mammals are in the range of observed chronic effect concentrations, which may indicate the potential for adverse effects in wildlife caused by the observed environmental concentrations in biota in crop areas. According to US EPA (2009) risk assessment of dicofol use, risks to aquatic invertebrates, fish, aquatic-phase amphibians, terrestrial-phase amphibians and mammals were identified.

142. The available data demonstrate interactions with the endocrine system in a multitude of different tests and test systems. Findings from animal experiments show also adverse effects in endocrine organs and hormonal imbalances. Mixtures of pesticides including dicofol at their NOAEL and LOAEL administered to rats via the diet lead to impairment of sperm motility and effects on the estrous cycle, hormone levels, and number of developing ovarian follicles. Evidence for mixture toxicity has also been derived from an accidental spill of KelthaneR (a dicofol formulation, which contained DDT at concentrations as high as 15%, and DDT's metabolites, DDD, DDE, and chloro-DDT) leading to histological differences in gonads and a high mortality rate in embryos and neonates of alligators at the contaminated lake. A dramatic decline in the alligator population has been observed in the years after the spill. Therefore mixture toxicity of dicofol, ΣDDT and other organochlorines might be a cause of concern for humans and wildlife.

143. Subchronic and chronic toxicity studies of dicofol lead to toxic effects in target organs (liver, thyroid, adrenals, brain, heart, testes) of mammals at low concentrations (NOAEL 0.22 mg/kg). Neurotoxicity has been demonstrated in acute and subchronic studies. A series of mechanistic in vitro studies on endocrine disruption, enzyme induction intercellular communication, signal transduction and protein binding support evidence for adverse effects, which may lead to tumour promotion. Risk assessment for consumers clearly demonstrates exceedances of ADIs. Several epidemiological studies have noted associations between dicofol exposure and prostate cancer in men and leukemia, Hodgkins disease and autism disorders in children. Although limitations of these studies hinder causal associations they illustrate the concern that adverse effects associated with dicofol exposure might also occur in humans. Further mixture toxicity of dicofol, ΣDDT and other organochlorines is a cause of concern for human and wildlife.

4. Concluding statement

144. Dicofol is restricted or prohibited in many countries and generally usage as a pesticide has markedly decreased in the last decade and was below 1,000 tonnes in 2012.

145. [Dicofol can be atmospherically transported to areas far from local sources, including Arctic and subarctic regions]. Dicofol and its transformation products are persistent in the environment and fulfil the persistency criterion of Annex D (under acidic conditions). Dicofol fulfils the bioaccumulation criterion of Annex D based on high BCF values in aquatic species.

146. Dicofol is highly toxic to the aquatic environment and toxic for reproduction in birds. Dicofol has been shown to be neurotoxic in mammals; it further affects the thyroid, the liver and the adrenals. There is evidence suggesting the relevance of adverse effects on humans. Endocrine related effects were reported in a series of in vitro assays. Indications from animal experiments showing adverse effects in endocrine organs, reproductive development and hormonal imbalances. A risk assessment based on exposure scenarios in various countries clearly demonstrates a risk for consumers (up to 1379% of ADI). Further the toxicity of mixtures of dicofol, DDT and other organochlorines is a cause of concern for humans and wildlife.

147. [Based on its inherent properties and taking into consideration the toxicity of mixtures of organochlorine compounds, dicofol as a result of its long-range environmental transport, is likely to lead to significant adverse human health and environmental effects, such that global action is warranted.]

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